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Vol. XXIV, No. 5 MAY, 1935

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

TRADE MARK

CONTENTS

Frontispiece and Sketch—A. O. Mickelsen 347
Editorial:
- International Congress of Military Medicine and Pharmacy 348
- The Pharmacist in Literature and the Museum of the American Institute of Pharmacy 348
- Federal Drug Legislation Must Not Be Permitted to Die—Fischelis 349
- Third Notice from the Committee on Transportation—Bradley 350

Scientific Section:
- Alkaloidal Reagents. VII. The Detection of Thallium—Munch and Ward 351
- Local Anesthetics—Phenyl Procaine—Braker and Christiansen 358
- Acyl Derivatives of Ortho-Aminophenol—Pollard and Forsee, Jr. 363
- The Potency of Oregon Digitalis—Lee and Stuhr 367
- Studies on the Bioassay of Digitalis—Defandorf 369
- The Rectal Absorption of Digitalis in Cats—Purdum 374
- Non-Heptane Constituents of Digger Pine (Pinus Sabinana)—Uhl 380
- Russian Ergot—Rusby 382
- Study of Germicidal and Antiseptic Activity of Some Mercury Compounds—Moness, Harris and Christiansen 386
- Vegetable Extracts and Blood-Sugar—Jorgensen and Lynn 389
- Suggestions for the Improvement of Professional Relations between Dentists and Pharmacists—Whitman, D.D.S. 392
- The Successful Application of U. S. P. and N. F. Publicity in a Retail Pharmacy—Williams 395
- A Pharmaceutical Study of p_H—Johnson 397

The Department of the American Association of Colleges of Pharmacy:
- The Teaching of Habitats in Pharmacognosy—Wirth 413
- Teaching Urinalysis to Students of Pharmacy—Greene 414
- Comments on Paper by Professor Antoine E. Greene on "Teaching Urinalysis to Students of Pharmacy"—Gershenfeld 417

Proceedings of the Local Branches 420
Association Business 426
Editorial Notes 429
Personal and News Items 430
Obituary 431
Societies and Colleges 433
Legal and Legislative 435
Book Notices and Reviews 438
Notice to Contributors to the Journal American Pharmaceutical Association 440
Pharmaceutical Abstracts 69–104
Advertising—Cover Pages 2, 3 and 4 and pp. I–XXIV.

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THE 83rd ANNUAL MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION WILL BE HELD IN PORTLAND, ORE., AUGUST 5–10, 1935.

Local Secretary, A. O. Mickelsen, N. E. 6th Ave. at Oregon St., Portland, Ore., Hotel Multnomah, Headquarters.

The 1935 Meetings of the American Association of Colleges of Pharmacy, the National Association of Boards of Pharmacy, Conference of Pharmaceutical Association Secretaries, of the Pharmaceutical Law Enforcement Officials and the Plant Science Seminar will also be held in Portland.

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E. F. KELLY, Secretary,
2215 Constitution Ave.,
Washington, D. C.

PLANT SCIENCE SEMINAR.

PORTLAND MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

The 13th annual meeting of the Plant Science Seminar will be held at North Pacific College, Portland, Ore. Announcements regarding the tour have been sent out, much information is given in the April JOURNAL and further details may be obtained by addressing the Local Secretary, Dean A. O. Mickelsen, N. E. 6th Ave. at Oregon, Portland, Ore.

The local committee is planning a program of field trips, lectures and visits of interest in the vicinity of Portland. The Seminar will make a two-day trip to Corvallis, stopping at points of interest under the direction of Prof. E. T. Stuhr. The local flora of Willamette Valley will be studied and a visit made to the drug farms where Hydrastis, Ginseng and Peppermint are cultivated.

OREGON SCENERY.

It is inherent in Americans to love the mountains, nature's wilds that endure down through the centuries. Oregon has its Coast Range, the Cascades, the Siskiyous, the Blue Mountains and other lesser groups. Here deep in the forests, in flower-covered meadows that nestle high above the world, alongside of lakes that dot the mountains like jewels inset in this wondrous panorama of nature, one may forget the troubles of the outside world. In fact, he can forget that any other world except this new one of peace and supreme contentment exists.

Crater Lake in Southern Oregon, a day's journey from Portland, is alone worth a trip across the continent; a miniature sea of sapphire, a jewel of wondrous blue set deep down in a rocky clasp of the Cascade mountains.

Go to the ends of the earth and nowhere will you find a body of water that matches it in magnificence and beauty. Neither is there any lake that matches it geologically.

Portland's parks, some with their natural lakes and virgin timber that has been preserved within their borders and beautified by wondrous rose gardens, other plants and shrubbery, are themselves worth a day of your time.

INFORMATION.

For information relative to program, rates and routes address the local committee or E. N. Gathercoal, 701 So. Wood St., Chicago; H. C. Christensen, 130 No. Wells St., Chicago; C. B. Jordan, Purdue University, La Fayette, Ind.; F. H. Eby, 1808 Spring Garden St., Philadelphia, Pa.; F. J. Bacon, Western Reserve University, Cleveland, Ohio.

See JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION for April and in this issue of the JOURNAL.

A. O. MICKELSEN.

JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION

VOL. XXIV MAY, 1935 No. 5

THE LOCAL SECRETARY OF THE PORTLAND MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

This brief sketch introduces the local secretary, A. O. Mickelsen, of the AMERICAN PHARMACEUTICAL ASSOCIATION for the meeting to be held in Portland, Ore., August 5th–10th.

Prior to the World War, Mr. Mickelsen specialized in commerce and public accounting, but due to an injury sustained during service, he concluded to engage in other activities and chose pharmacy; his training includes a college course in law. He became associated with the School of Pharmacy, North Pacific College of Oregon; for six years he served as instructor, then advanced to professor and, later, was elected dean.

It was largely through his efforts that a branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was organized in Portland. When the American Medical Association held its meeting in Portland (1928) Dean Mickelsen was chairman of the U. S. P. exhibit which was awarded the national certificate of merit for an outstanding educational display of the convention. He has been active in radio talks and publicity in behalf of professional pharmacy and was local chairman of Pharmacy Week. He has been associated with Kappa Psi for more than twelve years, for two years he served as satrap of the Northwestern Province and was instrumental in installing Pi Chapter of Rho Chi at the North Pacific College and is grand regent of Kappa Psi.

Dean Mickelsen is deeply interested in advancing the professional relations of dentistry and pharmacy; he is vice-president of the American Association of Colleges of Pharmacy, state chairman of food and drug legislation, representing the former association, and president of the North Pacific branch, A. PH. A. He was a member of the committee of five members who compiled the Pacific Drug Review prescription schedule.

He is a member of Post No. 1 of the American Legion, Portland, Ore.

EDITORIAL

E. G. EBERLE, EDITOR 2215 Constitution Ave., WASHINGTON, D. C.

INTERNATIONAL CONGRESS OF MILITARY MEDICINE AND PHARMACY.

IN former years no funds were available for delegates to the International Congress of Military Medicine and Pharmacy. Funds are to be provided this year by the adoption of a resolution submitted by the Committee on Foreign Affairs, providing for an appropriation of $8000.00 or so much thereof as may be necessary for expenses of participation by the United States in the 8th International Congress of Military Medicine and Pharmacy to convene at Brussels in June 1935.

Comment on prior meetings was made in the April JOURNAL. Secretary Cordell Hull believes that no less than 10 delegates should be sent from the United States and, certainly, pharmacy should be represented.

The Congress of Pharmacy convenes in Brussels on July 30th, and a very interesting program has been prepared, which was published in the *Journal de Pharmacie de Belgique*. There is more or less of a relationship between the two organizations and presents the opportunity for representation at both conventions. A wide range of papers has been listed for the Congress of Pharmacy, some of which may find application in the International Congress of Military Medicine and Pharmacy, thus, a paper by A. J. J. Van der Velde on "Research on the Sterilization and Biochemical Control of Pharmaceutical Products," "The Toxicity of Certain Insecticides," ably presented by Dr. Hampshire and Professor Schoofs, and quite a number of subjects were discussed by pharmacists at earlier Congresses; among the latter, the preparation of tablets, ampuls, methods of sterilization were shown, and a motor pharmacy demonstrated. European pharmacy was heretofore represented, but the writer's records do not show participation by American pharmacists.

THE PHARMACIST IN LITERATURE AND THE MUSEUM OF THE AMERICAN INSTITUTE OF PHARMACY.

THE *Bulletin de la Société d'Histoire de la Pharmacie* (France) for March presents a statement from the pharmacy of J. B. Caventou for "La Dame aux Camelias" from the collection of P. Lemay. The bill-head carries the inscription and face of the medal of award by the Royal Institute of France of the grand prize for the discovery of quinine sulphate by Pelletier and Caventou. There is further interest attached because only two of the novels of Dumas, the younger, survived, one of these "La Dame aux Camelias," from which book came the immortal drama by the same title.

In the Sunday *Times Herald* (Dallas, Tex.), April 21st, William D. Hornaday writes of an unfinished O. Henry story in a counter blotter of the drug store of J. J. Tobin, Austin, Texas, recently discovered. The story bears no title and is written in long hand by the author and reproduced in the *Times Herald*, but not reproduced in the JOURNAL at this time, because no reference is made of drugs. In Austin there abounds a wealth of O. Henryana; one of our fellow-members, the late H. L. Carleton, was manager of the Tobin drug store for a time; he informed the writer that years passed and O. Henry had left Texas before he knew William

Sydney Porter and O. Henry was the same person. It may be of interest to note that this master of the American short story selected as his *nom de plume* a name from the U. S. Dispensatory under Diluted Hydrocyanic Acid, that of O. Henry, referred to in connection with a proposed test; perhaps Porter was looking up data on poisons to be used in his writings.

Through a grant from the Carnegie Corporation and with the coöperation of the School Art League, the Folk Arts Museum at Riverdale is open to the public; Mrs. Eli Nadelman is the director. Walter Rendell Storey contributed an illustrated article to the *New York Times Magazine* for April 28th on the museum, in which are ensembles of furnishings, including an early American Pharmacy, with shelves, counters, bottles, jars, some still full of old herbs and drugs. Other types of displays are described.

These comments are made to enlist the interest of possible contributors to the museum of the American Institute of Pharmacy, where the history of American pharmacy should be arranged and displayed.

FEDERAL DRUG LEGISLATION MUST NOT BE PERMITTED TO DIE.

BY ROBERT P. FISCHELIS.*

As usually happens about this time of the year in matters of controversial Federal legislation, the situation with reference to Food and Drug legislation has reached a point where proponents, opponents and those who favor revision in part, must either effect compromises on disputed points or demonstrate that one or another group has marshaled sufficient support to be able to win when the matter comes to a vote in the Senate and House of Representatives. The only other alternative is to allow this proposed legislation to die and perhaps revive it at a later session of the Congress.

It appears to impartial observers that neither the proponents of the present Copeland bill nor its opponents nor those favoring partial revision can get all they want. Certain amendments introduced by Senator Bailey of North Carolina and others proposed by Senator Clark of Missouri have met opposition by Senator Copeland It is somewhat difficult to decide on what basis and in whose behalf some of the proposed amendments have been offered because there has been much "under cover" activity in connection with this legislation.

All of this must seem rather confusing to consumers of foods and drugs and to those producers and distributors who have no particular axe to grind and who can meet practically any standard which the Government might set with respect to quality, labeling, advertising or distribution of their product.

It is difficult to understand why minority groups, whose chief interest in food and drug legislation is to block efforts to compel truthful labeling and advertising of foods and drugs and to ease the path of fakers in the food and drug industries, should be in a position to thwart the efforts of earnest legislators and respectable citizens in providing proper control of the manufacture and distribution of drug products.

---

* President, AMERICAN PHARMACEUTICAL ASSOCIATION.

The answer is to be found in the peculiar partnerships which spring up between respectable members of industries and their predatory competitors when they either believe or are stampeded into believing that they are menaced by a common enemy. For example, one can hardly conceive of certain manufacturers of prescription products lining up with patent medicine manufacturers against the Government in matters of drug legislation when it is remembered how strongly the first-named group endeavors to emphasize to the medical and pharmacal professions and to the public its highly ethical conception of the function of drug manufacturers in the field of medical care. Again, it is difficult to understand why patent medicine manufacturers, after proclaiming the establishment of a self-imposed censorship of their advertising and engaging supposedly competent medical and technical advisers to keep themselves out of trouble, should oppose legislative confirmation of this admittedly necessary activity which would extend its benefits to all members of the industry and to all consumers of drugs and medicines.

What is there in the record of Food and Drug law enforcement by the Federal Government for the past thirty years that justifies any lack of confidence or the withholding of sufficient power to protect the public against the vicious and unethical practices which the proposed food and drug law prohibits?

American pharmacy and the drug industry simply cannot afford to allow the proposed legislation to die. The onus of failure to pass adequate legislation at this session must not be laid at our doorstep. It is not only fair play for the public and fair play for honest manufacturers and distributors of drugs and medicines but also extremely expedient for the drug industry to advocate "action and action now" on the bill without interposing further impossible conditions of compromise. Let it not be said that American consumers of foods and drugs have been deprived of proper protection against charlatans and betrayers of the confidence of the readers of our popular magazines and listeners to radio-broadcasts because the drug industry of the United States gave aid and comfort to its moral outlaws by objecting to regulations which are in the public interest.

THIRD NOTICE FROM THE COMMITTEE ON TRANSPORTATION.

T. J. BRADLEY, CHAIRMAN.

Several tours to Alaska will be available at the close of the Portland meeting of the ASSOCIATION. These include 9-day tours from Seattle to Skagway at eighty-five dollars for fare, meals and berth, and there will be no additional railroad fare to Seattle for those who are returning by way of that city, and several more extensive tours are available at proportional rates. Inquiries about these tours should be addressed to Local Secretary A. O. Mickelsen, N. E. 6th Ave., at Oregon, Portland, Oregon.

Several suggested routes, to and from Portland, were given in the April number of the JOURNAL, and the rates for the round trip, going by way of these or other routes and returning by another route are very low. It is not likely that we shall ever have a more favorable opportunity to visit the far west, and it should not be missed. Certificates will not be needed this year, to secure the low excursion rates, and any tourist agents will be able to give the members exact rates from their home cities, with other particulars.

SCIENTIFIC SECTION

BOARD OF REVIEW OF PAPERS.—*Chairman*, F. E. Bibbins, George D. Beal, L. W. Rising, H. M. Burlage, L. W. Rowe, John C. Krantz, Jr., Heber W. Youngken.

ALKALOIDAL REAGENTS. VII. THE DETECTION OF THALLIUM.*

BY JAMES C. MUNCH[1] AND JUSTUS C. WARD.

In connection with our studies on thallium the need arose for rapid, sensitive, specific methods of qualitative detection and of quantitative determination, in tissues, plants, soils and various types of products.

Thallium forms two series of compounds, being monovalent and trivalent. In general the trivalent or thallic compounds are unstable, being reduced to the thallous products. Commercial material used for cosmetics, medicinal and rodenticidal purposes is almost entirely thallous thallium.

In the flame, thallium compounds dissociate, liberating Tl which produces a characteristic green color and spectrum. If this flame is allowed to strike on a cold surface, a brown mirror of Tl forms (73). In the Marsh apparatus the stain produced is similar to that produced by arsenic, but it gives a characteristic yellow color with iodine and is insoluble in ammonium sulphide (11). Spectroscopic studies of the emission spectra (67) show a number of characteristic lines, between 2552.9 Å. and 71170 Å. In the visible spectrum the line usually considered to be characteristic is at 5350.47 Å. Using the spectroscope, a number of qualitative investigations have been conducted (16, 25, 41, 43, 45, 51, 57, 72, 79, 82, 84, 99). The limit of sensitivity is reported to be 1 gamma, although Lamy claimed that he was able to detect 0.002 gamma of thallium by following the 5350 line. We have used the spectroscope in our investigations, but have also made a detailed search of the literature and a specific study of the more promising reactions with the view of developing quick methods to use when a spectroscope is not available. Our detailed results are given in Tables I and II.

TABLE I.—QUALITATIVE DETECTION OF THALLOUS THALLIUM.

No.	Name of Reagent.	Color in Solution.	Color of Precipitate.	Threshold, Mg. Tl/Cc.	Literature References.
1	H_2SO_4	None	None	....	.....
2	HNO_3	None	None	....	.....
3	Froehde	None	White	20	.....
4	Marquis	None	None	....	.....
5	Mayer	None	Curdy light yellow	0.2	.....
6	Dragendorff	None	Brown-black	2	.....
7	Wagner	None	Brown-black	2	.....
8	Picric acid	None	Yellow needles, prisms	20	(91)
9	$FeCl_3$	None	White needles	0.2	.....
10	$K_2Cr_2O_7$; NH_3	None	Orange-yellow cryst.	0.2	(91)
11	$K_4Fe(CN)_6$	None	Yellow	20	.....
12	" ; $Ca(CH_3COO)_2$	None	White	20	(1)
13	$KMnO_4$; HCl	Pink; none	Red-brown; white	0.2	(7, 17, 18, 42, 46, 58, 71, 104)

* Scientific Section, A. PH. A., Washington meeting, 1934.

[1] Bureau of Biological Survey, Glen Olden, Pennsylvania, and Denver, Colorado.

14	$PtCl_4$	None	Yellow octahedra	0.02	(3, 59, 80)
15	Schiebler	None	Yellow-white	2	.....
16	U Acetate	None; yellow	Yellow prisms	0.2	(19)
17	Mecke	None	None	....	.....
18	Millon	None	Yellow-white curd	0.2	.....
19	Na alizarin sulphonate, 0.5%	Dark blue	Blue-yellow	20	(40)
20	Alkanna; NH_3	Blue	None	....	(32)
21	Al	None	None	....	(59)
22	Al_2O_3	None	White prisms	0.2	(42)
23	$SbCl_3$; KI; dilute	None	Orange-yellow	0.2	(27)
24	K Antimonyl tartrate	None	White prisms	20	.....
25	Na_3AsS_3	None	None	....	(20)
26	As_2S_3; H_2S	None	Gray-black	0.2	.....
27	Benzidine	Blue	Blue	20	(29, 41)
28	Na benzoate	None	None	....	.....
29	$BiCl_3$	None	White	0.2	.....
30	Br; NH_3	None	White	0.2	(12, 89)
31	HBr	None	Pale yellow	2	(26, 59)
32	$NaBrO_3$ or $Mg(BrO_3)_2$	None	White	20	(58, 80, 89, 103, 106)
33	$CdCl_2$	None	White	0.2	.....
34	$Ce(SO_4)_2$,; $N/10$ HCl	Pale yellow	None	....	(6, 86, 103)
35	HCl	None	White	0.2	(3, 26, 59, 69)
36	$KClO_3$	None	None	....	.....
37	Citric acid	None	None	....	.....
38	$Na_3Co(NO_2)_6$, fresh 6%	None	Brick-red	0.2	(90, 95)
39	$Cr(NO_3)_3$ test paper	None	Green-yellow	20	(61)
40	K_2CrO_4	None	Yellow	0.2	(12, 14, 21, 41, 42, 55, 62, 63, 65, 66, 75, 81)
41	HCHO	None	Gray-white	20	.....
42	$K_4Fe(CN)_6$	Yellow	None	....	(4, 13, 33, 55, 80, 96, 97)
43	$AuBr_3$, fresh, hot	None	Yellow	20	.....
44	Hydroquinone	None	None	....	.....
45	HI	None	Yellow	0.2	(2, 3, 4, 11, 14, 22, 23, 26, 27, 31, 34–37, 41, 44, 47, 52–54, 58, 59, 67–71, 76, 85, 87, 88, 90, 97, 98, 102, 105)
46	NaIO	None	Dark brown	100	(101)
47	KIO_3; HCl	None	White plates	200	(5, 10, 24)
48	$Ir(NO_3)_3$	None	Yellow-white	....	(28)
49	NaF or NH_4F	None	Yellow-white	20	(106)
50	Mg	None	Black deposit	0.2	(90)
51	NH_4 Molybdate	None	White leaves	0.2	(38, 39, 91)
52	Sat. *a*-naphthol; dimethyl - *p* - phenylenediamine	None	None	....	(56)
53	Ozone	None	Brown	....	(83)
54	$PdCl_2$	None	Cinnamon-brown	0.2	.....

55	$AuPdCl_6$:HCl	None	Cinnamon-brown	0.2	(94)
56	Na_2HPO_4; alkaline soln.	None	White	20	(80)
57	KH_2PO_4:alkaline soln.	None	White	20	.....
58	Phosphomolybdic acid: HNO_3	None	Yellow	2	(38, 39, 74, 80)
59	Phosphotungstic acid	None	Milky white	0.2	.....
60	ReO_4:I_2	None	Dark plates	....	(49)
61	K_2ReBr_6	None	Violet	....	(48)
62	K_3ReCl_6	None	Dark brown	....	(48)
63	K_4ReCl_6	None	Brown-yellow	....	(48)
64	Saccharin	None	White rods, needles	20	(77)
65	Silicotungstic acid	None	Milky white	0.2	.....
66	$AgNO_3$; alkaline soln.	None	Dark brown	0.2	(100)
67	H_2S	None	Black	0.2	(15, 59, 64, 80, 82, 92)
68	S impurities in benzine; Tl ethylate	None	Orange	....	(50, 60)
69	S impurities in benzine; dimethyl-Tl-ethylate	None	Orange	....	(50, 60)
70	S impurities or CS_2; Tl acetyl-acetone	None	Orange	....	(30, 50)
71	S impurities or CS_2; Tl-yellow; CH_2Bz	None	Carmine	....	(30)
72	S impurities or CS_2; Tl-yellow; $AcCH_2Bz$	None	Cinnabar	....	(30)
73	CS_2; Tl-yellow; AcCH-MeBz	None	None	....	(30)
74	CS_2; Tl-yellow; $AcCH_2$-COCOOEt	None	None	....	(30)
75	CS_2; Tl-yellow; $BzCH_2$-COCOOEt	None	None	....	(30)
76	CS_2; Tl-yellow; EtO-$OCCOCH_2COOEt$	None	None	....	(30)
77	CS_2; Tl-yellow; $AcCH_2$-COOEt	None	Yellow	....	(30)
78	CS_2; Tl-yellow; $BzCH_2$-COOEt	None	Orange-red	....	(30)
79	CS_2; H_2S NH_3	None	Vermillion	0.2	(75)
80	KSCN	None	White prisms, needles	20	(91, 93)
81	$Na_2S_2O_3$	None	White prisms, rods	20	(9, 91)
82	Tartaric acid	None	White prisms	20	(91)
83	Tannic acid; NH_3	Red	Yellow-green	20	.....
84	TiO_2	None	None	....	.....
85	$SnCl_2$; KI	None	Dark yellow	0.2	(94)
86	$SnCl_2$; H_2S	None	Gray-white	0.2	(43)
87	Na Tungstate, 5%	None	White plates	20	(39)
88	Urea	None	None	....	.....
89	NH_4 metavanadate	None	None	....	.....
90	Zn	None	Black deposit	0.2	(59, 79, 80)

TABLE II.—QUALITATIVE DETECTION OF THALLIC THALLIUM.

No.	Name of Reagent.	Color in Solution.	Color of Precipitate.	Threshold, Mg. Tl/Cc.	Literature References.
1	H_2SO_4	None	None	..	.....
2	HNO_3	None	None	..	.....
3	Froehde	None	None	..	.....
4	Marquis	None	None	..	.....

5	Mayer	None	None	..	.....
6	Dragendorff	None	None	..	.....
7	Wagner	None	None	..	.....
8	Picric acid	None	None	..	.....
9	$FeCl_3$	None	None	..	.....
10	$K_2Cr_2O_7$	None	None	..	.....
11	$K_4Fe(CN)_6$	None	None	..	.....
12	$KMnO_4$	None	None	..	.....
13	$PtCl_4$	None	None	..	.....
14	Schiebler	None	None	..	.....
15	U Acetate	None	None	..	.....
16	Mecke	None	None	..	.....
17	Millon	None	None	..	.....
35	HCl	None	None	..	(3, 26, 59, 69)
45	HI	None	Yellow	20	(See Table I)
52	Sat. *a*-naphthol; dimethyl-*p*-phenylenediamine	Blue	None	20	(56)
64	Saccharin	None	None	..	.....
79	CS_2; H_2S; NH_3	None	Black	20	(75)
80	KSCN	None	Pale yellow	20	(91, 93)

It must be remembered that working conditions in various laboratories may influence the delicacy of response of these qualitative tests. We have suggested the approximate sensitivity of some of these reactions, solely as suggestion of their routine application, rather than as absolute limits for threshold reactions.

In making these tests, thallic sulphate and various thallous compounds were used (usually thallous sulphate). Since the atomic weight of thallium is 204.1 a normal solution would contain about twenty per cent of Tl. Our stock solutions were prepared as $N/10$ and $N/1000$ solutions with respect to Tl. When these solutions have given positive results, further dilutions have been prepared to determine the approximate threshold of sensitivity.

CONCLUSION.

Qualitative tests for thallium have been studied, using ninety reagents.

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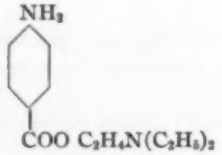
LOCAL ANESTHETICS—PHENYL PROCAINE.*

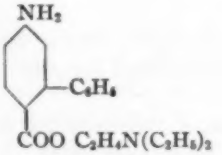
BY W. BRAKER AND W. G. CHRISTIANSEN.[1]

This investigation concerns the study of phenyl derivatives of procaine (I) and its analogues. The study was initiated by the comparatively greater activity and lesser toxicity of *o*-phenyl phenol over phenol. The substitution of a phenyl group on the benzene nucleus of procaine would yield, it was expected, a substance of greater potency and lesser toxicity than the parent substance. A summary of the biological activity of the various substances prepared is contained below.

The initial substance synthesized was phenyl procaine (II). The details of the preparation of (II) are stated in the experimental section. Essentially, the



(I)



(II)

synthesis employed was the preparation of 2-carboxy 5-amino diphenyl and the subsequent reaction of its sodium salt with β-diethylamino ethyl chloride. Phenyl procaine is an active anesthetic but due to such factors as precipitation upon the addi-

* Section on Practical Pharmacy and Dispensing, Madison meeting, 1933.

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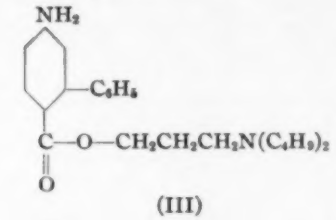
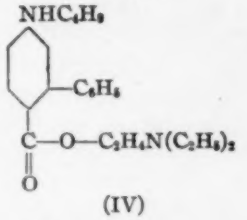
tion of buffers and irritation in corneal and intradermal tests, the compound does not appear to be of value.

Analogues of phenyl procaine were synthesized for the purpose of

(1) Determining the effect of increasing the size of the dialkylamino alkyl group (III).
(2) Ascertaining the effect of alkylating the amino group (IV).
(3) Investigating the effect of halogenation, as depicted by (V).
(4) Observing the effect of the elimination of the amino group (VI).



(III)



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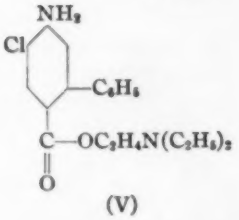

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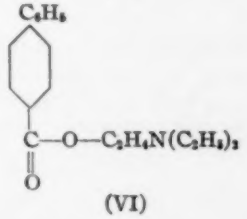
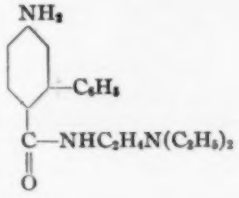


(VI)

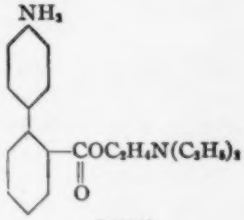
The hydrochlorides of the above compounds were either too acid for testing (IV and VI) or too inactive (III and V) to warrant any further investigation.

A compound containing a β-diethylamino ethyl carbamido group (VII) which is present in percaine was also prepared but was comparatively inactive.

The effect of shifting the amino group from the 5- to the 4′-position was also studied. However, an aqueous solution of the hydrochloride of this substance (VIII) was comparatively inactive.



(VII)



(VIII)

EXPERIMENTAL.

2-p-Toluenesulphonamidodiphenyl (1).—Prepared from 2-amino diphenyl and *p*-toluenesulphon chloride. M. p., 96° C.

5-Nitro 2-p-Toluenesulphonamidodiphenyl (2).—Prepared by nitration of 2-*p*-toluenesulphonamido diphenyl. M. p. 168–169° C.

2-Amino 5-Nitro Diphenyl (3).—Prepared by hydrolysis of 2-*p*-toluenesulphonamido 5-nitro diphenyl with concentrated sulphuric acid. M. p. 123–125° C.

2-Cyano 5-Nitro Diphenyl.—The best procedure for the preparation of the substance requires diazotization of 2-amino 5-nitro diphenyl in *concentrated hydrochloric acid*. Diazotization in dilute hydrochloric acid and subsequent substitution of the diazonium group leads to a reduced yield.

Fifty Gm. of 2-amino 5-nitro diphenyl was suspended in 130 cc. of concentrated hydrochloric acid and was diazotized with 21.5 Gm. of sodium nitrite contained in 70 cc. of water. The diazonium solution is then added at −10° to 0° C. to a solution of potassium copper cyanide which had been prepared by adding 120 Gm. of potassium cyanide in 250 cc. of water to 100 Gm. of crystalline copper sulphate contained in 250 cc. of water. The addition of the diazonium solution was made over a period of 30 minutes using stirring. The suspension thus obtained was stirred at 0° C. for one hour when the temperature was slowly raised to 20° C. and held at the latter temperature for $^1/_2$ hour. The suspension was then slowly heated to 90° C. and kept at this temperature for 3 hours. The reaction mixture was carefully alkalinized with 150 cc. of 40% sodium hydroxide. A brown precipitate was obtained which was filtered off, washed with water and dried *in vacuo*. The substance was twice recrystallized from alcohol.

Yield, 43 Gm. of small, needle-like brown crystals −80%.
Melting point, 131–133° C.
Assay—Nitrogen found, 11.90%.
Calculated for $C_{13}H_8O_2N_2$, 12.50%.

2-Carboxy 5-Nitro Diphenyl.—This substance was obtained by hydrolysis of 2-cyano 5-nitro diphenyl.

Five and two-tenths Gm. of the cyano compound was suspended in a mixture of 75 cc. of glacial acetic acid, 60 cc. of sulphuric acid and 50 cc. of water and refluxed for 8 hours. The mixture was then cooled and diluted with an equal volume of water. The white crystals obtained were filtered, washed with water and dried *in vacuo*.

Yield, 3.5 Gm.; 62%.
Assay—Nitrogen found, 5.78%.
Calculated for $C_{13}H_9O_4N$, 5.76%.

2-Carboxy 5-Amino Diphenyl Hydrochloride.—Three Gm. of 2-carboxy 5-nitro diphenyl was reduced with 10 Gm. of tin and 50 cc. of hydrochloric acid. The reduction was carried on for 3 hours; the solution was then diluted with water and the tin precipitated with hydrogen sulphide. The sulphide was filtered off and the filtrate was concentrated. When cooled, the solution deposited 2-carboxy 5-amino diphenyl hydrochloride as silvery plates.

Yield, 1.3 Gm.
Melting point, 230° C.
Analysis—Nitrogen found, 5.42%.
Calculated for $C_{13}H_{12}O_2NCl$, 5.61%.

2-β-Diethylamino Carbethoxy 5-Amino Diphenyl.—One and two-tenths Gm. of 2-carboxy 5-amino diphenyl hydrochloride was dissolved in 20 cc. of absolute alcohol and a solution of 0.22 Gm. of sodium in 20 cc. of alcohol was added. The sodium chloride which precipitated was removed by filtration and 1.0 Gm. of β-diethylamino ethyl chloride in 10 cc. of alcohol was added to the filtrate; this alcoholic solution was refluxed for 7 hours. The solvent was then removed by distillation *in vacuo*. The residue was a light yellow oil which was converted to its dihydrochloride by passing dry hydrochloric acid gas into its ethereal solution. A yellow oil separated which, after pouring off the ether, was heated in an oven at 100° C. for 2 hours. It was then placed in a vacuum desiccator over calcium chloride and sodium hydroxide. The dihydrochloride thus obtained was a yellowish white substance which was hygroscopic.

Analysis—Nitrogen found, 7.29%.
Calculated for $C_{19}H_{28}N_2O_2Cl_2$, 7.27%.
Chlorine found, 18.34%.
Calculated for $C_{19}H_{28}N_2O_2Cl_2$, 18.44%.

The borate of the base was obtained by evaporating to dryness an aqueous solution of 1.6 Gm. boric acid and 1.1 Gm. of base. A yellowish white powder was obtained.

Analysis—Nitrogen found, 4.87%.
Calculated for $C_{19}H_{39}O_{17}B_4N_2$, 4.51%.

2-Di-n-Butylamino Carbopropoxy 5-Amino Diphenyl.—One and one-tenth Gm. of 2-carboxy 5-amino diphenyl hydrochloride was dissolved in 20 cc. of absolute alcohol and a solution of 0.2 Gm. of sodium in 20 cc. of alcohol was added. The sodium chloride formed was filtered off. The filtrate was added to a solution of 0.92 Gm. of di-*n*-butylamino propyl chloride in 30 cc. of alcohol. The solution was refluxed for 7 hours after which the sodium chloride formed was filtered off and the filtrate was distilled *in vacuo* to remove the solvent. The residue was a dark brown oil which was 2-di-*n*-butylamino carbopropoxy 5-amino diphenyl.

Analysis—Nitrogen found, 6.97%.
Calculated for $C_{24}H_{34}O_2N_2$, 7.33%.

The dihydrochloride was obtained by evaporating an alcoholic hydrochloric acid solution of the base *in vacuo*. It was a dark brown, brittle substance.

Analysis—Chlorine found, 15.94%.
Calculated for $C_{24}H_{36}O_2N_2Cl_2$, 15.71%.

2-Phenyl 4-Amino Benzoyl Chloride.—Two and seven-tenths Gm. of 2-carboxy 5-amino diphenyl was dissolved in 30 cc. of benzene and 5.0 Gm. of thionyl chloride was added. The solution was refluxed for 3 hours after which the benzene and excess thionyl chloride were removed by distillation *in vacuo*, leaving an oily residue. The latter was distilled at 2–3 mm. at which pressure 2-phenyl 4-amino benzoyl chloride distilled at 175–183° C. It was a yellow oil.

Yield, 2.5 Gm.
Analysis—Chlorine found, 15.49%.
Calculated for $C_{13}H_{10}ONCl$, 15.33%.

2-β-Diethylamino Ethyl Carbamido 5-Amino Diphenyl Hydrochloride.—Three and four-tenths Gm. of 2-phenyl 4-amino benzoyl chloride was dissolved in 30 cc. of dry benzene and reacted with 2.0 Gm. (20% excess) of unsymmetrical diethylethylene diamine contained in 25 cc. of benzene. The reaction mixture warmed up rapidly; it was refluxed for 3 hours. A solid separated out during refluxing. The isolation was made by pouring off the benzene from this solid and dissolving the latter in dilute hydrochloric acid. The acid solution was decolorized with charcoal and was evaporated to dryness *in vacuo*. The product was an extremely hygroscopic, dark brown solid.

Analysis—Nitrogen found, 12.45%.
Calculated for $C_{19}H_{28}N_3OCl$, 12.09%.
Chlorine found, 10.84%.
Calculated for $C_{19}H_{28}N_3OCl$, 10.23%.

A borate was also prepared; it also was hygroscopic and was not further investigated.

2-Carboxy 5-Butylamino Diphenyl.—Two and two-tenths Gm. of 2-carboxy 5-amino diphenyl was dissolved in 10 cc. of toluene and refluxed with 1.5 Gm. of *n*-butyl bromide. After 6 hours the toluene and excess butyl bromide were removed by distillation *in vacuo*. An alcoholic solution of the residual semi-solid substance was decolorized with charcoal and evaporated to dryness. The residue was a brown semi-solid.

Analysis—Nitrogen found, 4.96%.
Calculated for $C_{17}H_{19}O_2N$, 5.20%.

2-β-Diethylamino Carbethoxy 5-Butylamino Diphenyl.—2.35 Gm. of 2-carboxy 5-butylamino diphenyl was dissolved in 25 cc. of absolute alcohol and a solution of 0.22 Gm. of sodium in 12 cc. of alcohol was added, followed by 2 Gm. of β-diethylamino ethyl chloride in 10 cc. of alcohol. The solution was refluxed for 7 hours and then filtered from sodium chloride. The filtrate was decolorized with charcoal and 1 mol. of hydrochloric acid was added. By evaporating the solution to dryness *in vacuo* the mono-hydrochloride was obtained as a dark brown brittle substance.

Analysis—Nitrogen found, 6.56%.
Calculated for $C_{22}H_{33}N_2O_2Cl$, 6.92%.
Chlorine found, 8.90%.
Calculated for $C_{22}H_{33}N_2O_2Cl$, 8.78%.

2-Carboxy 4-Chlor 5-Amino Diphenyl Hydrochloride.—Two and two-tenths Gm. of 2-carboxy 5-amino diphenyl hydrochloride was dissolved in 25 cc. of glacial acetic acid and then 1.8 Gm. of sulphuryl chloride was added. The solution was allowed to remain at 25° C. for 2 hours after which the acetic acid was removed by distilling *in vacuo*. The last traces of acetic acid were removed by heating with alcohol and subsequently distilling. The residue was a light brown solid.

Analysis—Chlorine found, 25.39%.
Calculated for $C_{13}H_{10}O_2Cl_2N$, 25.08%.

A portion of this substance was oxidized with alkaline permanganate solution. A small quantity of benzoic acid was isolated and identified by melting point. This indicated that the position of the chlorine atom was in the substituted benzene nucleus.

2-β-Diethylamino Carbethoxy 4-Chlor 5-Amino Diphenyl Dihydrochloride.—One and three-tenths Gm. of the sodium salt of 2-carboxy 4-chlor 5-amino diphenyl was refluxed with 1.2 Gm. of β-diethylamino ethyl chloride in alcohol for 5 hours. The isolation was made as in the preparation of 2-β-diethylamino carbethoxy 5-amino diphenyl. A light yellow oil was obtained which was converted to its dihydrochloride by evaporating its alcoholic–hydrochloric acid solution to dryness *in vacuo*. A brown hygroscopic substance was obtained.

Analysis—Nitrogen found, 7.08%.
Calculated for $C_{19}H_{25}N_2O_2Cl_3$, 6.67%.
Chlorine found, 16.22%.
Hydrochloride chlorine calculated for $C_{19}H_{25}N_2O_2Cl_3$, 16.92%.

2-Cyano 4′-Nitro Diphenyl.—The substance was prepared by the same procedure used for 2-cyano 5-nitro diphenyl. A dark brown substance was obtained in a 30% yield.

Analysis—Nitrogen found, 11.93%.
Calculated for $C_{13}H_8N_2O_2$, 12.50%.

2-Carboxy 4′-Nitro Diphenyl.—This substance was prepared by the hydrolysis of 2-cyano 4′-nitro diphenyl by the same procedure used for hydrolyzing 2-cyano 5-nitro diphenyl. A dark brown substance was isolated in a 54% yield.

Analysis—Nitrogen found, 5.93%.
Calculated for $C_{13}H_9O_4N$, 5.76%.

2-Carboxy 4′-Amino Diphenyl Hydrochloride.—This was prepared by reduction of 2-carboxy 4′-nitro diphenyl by tin and hydrochloric acid. A dark brown, feathery substance was obtained.

Analysis—Nitrogen found, 5.38%.
Calculated for $C_{13}H_{12}O_2NCl$, 5.61%.

2-β-Diethylamino Carbethoxy 4′-Amino Diphenyl Dihydrochloride.—The method employed was identical with that used in the preparation of 2-β-diethylamino carbethoxy 5-amino diphenyl dihydrochloride. A dark brown semi-solid substance was obtained.

Analysis—Nitrogen found, 7.70%.
Calculated for $C_{19}H_{26}O_2N_2Cl_2$, 7.27%.
Chlorine found, 18.48%.
Calculated for $C_{19}H_{26}O_2N_2Cl_2$, 18.44%.

4-Cyano Diphenyl (*4*).—The substance was prepared according to Kaiser's method (5). M. p. 79° C.

4-Carboxy Diphenyl (*6*).—The hydrolysis of 4-cyano diphenyl yielded the substance. M. p. 220° C.

4-β-Diethylamino Carbethoxy Diphenyl Hydrochloride.—This substance was obtained by refluxing sodium *p*-phenyl benzoate with diethylamino ethyl chloride and subsequently covering the base to its hydrochloride by methods mentioned above.

Analysis—Chlorine found, 10.29%.
Calculated for $C_{19}H_{24}O_2NCl$, 10.64%.

Anesthetics Tests.—The biological results have indicated that phenyl procaine is considerably more active than cocaine hydrochloride and novocaine. This fact is borne out by the following table denoting the concentrations required for equivalent duration of anesthesia by intradermal injection into guinea pigs.

TABLE I.

	Required Concentration of the Dihydrochloride.		
Duration of Anesthesia.	Phenyl Procaine.	Cocaine.	Procaine.
50 Minutes	0.73%	1.01%	2.1%
35 Minutes	0.40%	0.52%	1.0%

Phenyl procaine hydrochloride was also more active on the rabbit's cornea although it was slightly irritating.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

SUMMARY.

In a series of phenyl derivatives of procaine the most active is the hydrochloride of β-diethylamino ethyl 2-phenyl 4-amino benzoate.

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ACYL DERIVATIVES OF ORTHO-AMINOPHENOL.*

BY C. B. POLLARD AND W. T. FORSEE, JR.

When diacyl derivatives of *o*-aminophenol were prepared by the usual methods, it was found in many cases that the order of introduction of the two different acyl groups has no influence upon the formation of the diacyl, identical products being isolated from the two acylations. The formation of identical rather than isomeric products on reversing the order of acylation indicated that during acylation a rearrangement must have occurred in one of the two cases. The positions of the acyl groups of the molecule were determined by removing the group attached to the oxygen by saponification with dilute alkali, and determining from the physical constants of the remaining monoacylated product the group attached to the nitrogen. The formation of isomeric diacyls and the production of the same

* Contribution from the Chemical Laboratories, College of Pharmacy, University of Florida.

saponification product indicates that a rearrangement must have occurred during saponification.

Considerable experimental evidence has indicated that certain acyl groups have more influence than others in bringing about this migration, weight and the acidity of the groups being considered to have the predominating influence in their obtaining a position in the more basic amino group.

Previous work on this subject by Ransom (1), Ransom and Nelson (2), Nelson and others (3, 4, 5, 6, 7), Raiford and others (8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18) and Bell (19, 20) is discussed in the literature.

The work of Pollard and others (21, 22) using one particular acyl chloride as one of the acylating agents in each diacyl throughout each series of experiments, indicated that relative acidity and weight of the acyl groups are not the controlling factors in this type of rearrangement.

This investigation was carried out in order to study further the effect of these factors on rearrangement. The acylating agent, *o*-*n*-heptanoyl chloride, was kept constant throughout the series. This selection afforded a heavy group and one which was less acidic than any group against which it was introduced. Diacyls were prepared by introducing the heptanoyl group against the *n*-butyryl, *n*-valeryl, *n*-caproyl, phenylacetyl and hydrocinnamyl groups.

Regardless of the order of introduction, the *n*-heptanoyl and *n*-valeryl groups produced diacyls whose melting points and mixed melting points indicated that one or both of the compounds was a mixture of the two possible isomers. Saponification of each of these diacyls yielded only *o*-*n*-heptanoylaminophenol, indicating in one case the migration of the *n*-heptanoyl group from the oxygen to the nitrogen. Similar results were obtained with diacyls in which the acylating groups were *n*-heptanoyl and *n*-caproyl. The acylation and saponification of these isomers involved rearrangements in which the *n*-heptanoyl group replaced the lighter and more acidic *n*-valeryl and *n*-caproyl groups.

o-*n*-Heptanoylaminophenol acylated with *n*-butyryl chloride gave a compound which was distinctly different from that obtained by the acylation of *o*-*n*-butyrylaminophenol with *n*-heptanoyl chloride. However, both isomeric diacyls yielded the same saponification product, *o*-*n*-heptanoylaminophenol. Similar results were obtained with diacyls in which the acylating groups were *n*-heptanoyl and phenylacetyl. The saponification of these isomers involved rearrangements in which the *n*-heptanoyl group replaced the lighter and more acidic *n*-butyryl group and the heavier and more acidic phenylacetyl group.

Introduction of the *n*-heptanoyl and hydrocinnamyl groups resulted in the production of the equilibrium mixtures of the two possible diacyls regardless of the order of introduction. Saponification in each case, also gave mixtures composed of approximately 50% of each of the possible monoacyls, showing that a partial rearrangement had occurred in each case.

EXPERIMENTAL.

o-*n*-Heptanoylaminophenol and *o*-*n*-caproylaminophenol were prepared by the method of Groenvik (23) using *o*-aminophenol and the acid chloride in an anhydrous ether solution. Their properties are summarized in Table I. The other monoacyls used, which have been previously described, were made by the same method.

TABLE I.—PROPERTIES OF MONOACYLS.

	1.	2.
Name	*o-n*-Heptanoylaminophenol	*o-n*-Caproylaminophenol
Formula	$C_6H_{13}CONHC_6H_4OH$	$C_5H_{11}CONHC_6H_4OH$
M. p., ° C.	85.5–86.5	80.0–80.5
Yield, %	96.00	95.00
N, % calculated	6.33	6.76
N, % found	6.18	6.76
C, % calculated	70.56	69.51
C, % found	70.64	69.46

o-n-Heptanoylaminophenyl n-valerate ($C_6H_{13}CONHC_6H_4OCOC_4H_9$).—To 5 Gm. of *o-n*-heptanoylaminophenol was added 2.7 Gm. of *n*-valeryl chloride. After the addition of 2 drops of concentrated sulphuric acid, the mixture was heated on a water-bath for 5 hours. A yellow oil was formed. The product was washed thoroughly with hot water and, after repeated recrystallization from hot 80% alcohol and cooling in an ice salt bath, it solidified in white crystals melting at 37.5–38.5°.

About 0.5 Gm. of this compound was saponified with a small quantity of a 10% potassium hydroxide solution. After complete solution had taken place, the mixture was filtered, cooled and acidified with dilute hydrochloric acid. White crystals separated. This product was filtered, washed with water and recrystallized from dilute alcohol. A mixed melting point of this product with *o-n*-heptanoylaminophenol showed the two compounds to be identical.

Compounds listed in Table II as 2, 3, 4, 7 and 8 were prepared by this method which is a modification of that of Jacobs, Heidelberger and Rolf (24).

o-n-Heptanoylaminophenyl n-butyrate ($C_6H_{13}CONHC_6H_4OCOC_3H_7$).—A mixture of 5 Gm. of *o-n*-heptanoylaminophenol, 2.5 Gm. of *n*-butyryl chloride and 2 drops of concentrated sulphuric acid was placed in an anhydrous ether solution and refluxed on a water-bath for 2 hours. After evaporation of the ether, a pale yellow oil remained. This was thoroughly washed with hot water and, after cooling in an ice bath, the product solidified. It was recrystallized four times from hot 80% alcohol, being deposited in white crystals, m. p. 41.5–42.5°.

The compound listed in Table II as 6 was also prepared by this method. All diacyls were saponified in approximately the same manner as previously described.

o-n-Heptanoylaminophenyl hydrocinnamate ($C_6H_{13}CONHC_6H_4OCOCH_2CH_2C_6H_5$).—An excess (6 Gm.) of hydrocinnamyl chloride was added to a pyridine solution of 6.6 Gm. of *o-n*-heptanoylaminophenol. The mixture was refluxed on a water-bath for 4 hours. After allowing to stand over night, the mixture was diluted with several volumes of water. A red oil separated. This was filtered and washed thoroughly with a very dilute hydrochloric acid solution. The remaining oil was then washed with a 5% solution of ammonium carbonate. After thoroughly washing with hot water, the oily product was dissolved in a minimum quantity of hot 80% alcohol and allowed to crystallize in an ice salt bath. Red-brown crystals separated. After several such recrystallizations, a cream-colored product was deposited which melted at 47–50° C.

The compound listed in Table II as 10 was also prepared by this method which is that of Einhorn and Hollandt (25).

TABLE II.—DIACYL DERIVATIVES OF *o*-AMINOPHENOL.

	Name.	Formula.
1.	*o-n*-Heptanoylaminophenyl *n*-valerate	$C_6H_{13}CONHC_6H_4OCOC_4H_9$
2.	*o-n*-Valerylaminophenyl *n*-heptanoate	$C_4H_9CONHC_6H_4OCOC_6H_{13}$
3.	*o-n*-Heptanoylaminophenyl *n*-caproate	$C_6H_{13}CONHC_6H_4OCOC_5H_{11}$
4.	*o-n*-Caproylaminophenyl *n*-heptanoate	$C_5H_{11}CONHC_6H_4OCOC_6H_{13}$
5.	*o-n*-Heptanoylaminophenyl *n*-butyrate	$C_6H_{13}CONHC_6H_4OCOC_3H_7$
6.	*o-n*-Butyrylaminophenyl *n*-heptanoate	$C_3H_7CONHC_6H_4OCOC_6H_{13}$
7.	*o-n*-Heptanoylaminophenyl phenylacetate	$C_6H_{13}CONHC_6H_4OCOCH_2C_6H_5$
8.	*o*-Phenylacetylaminophenyl *n*-heptanoate	$C_6H_5CH_2CONHC_6H_4OCOC_6H_{13}$
9.	*o-n*-Heptanoylaminophenyl hydrocinnamate	$C_6H_{13}CONHC_6H_4OCOCH_2CH_2C_6H_5$
10.	*o*-Hydrocinnamylaminophenyl *n*-heptanoate	$C_6H_5CH_2CH_2CONHC_6H_4OCOC_6H_{13}$

	M. P., ° C.	Yield, %.	Analysis, N, %. Calcd.	Found.	Analysis, C, %. Calcd.	Found.
1.	38–39	15	4.58	4.38	70.76	70.28
2.	43.5–45	25	4.58	4.41	70.76	70.33
3.	37–38	20	4.38	4.30	71.42	71.61
4.	41–42.5	20	4.38	4.25	71.42	71.75
5.	41.5–42.5	61	4.80	4.56	70.05	70.01
6.	32.5–33.5	27	4.80	4.54	70.05	69.82
7.	69–69.5	44	4.12	3.87	74.29	74.08
8.	83–85	31	4.12	4.16	74.29	74.35
9.	47–50	62	3.96	3.73	74.74	74.85
10.	54–56.5	55	3.96	3.69	74.74	74.55

Saponification Product.

1. $C_6H_{13}CONHC_6H_4OH$
2. $C_6H_{12}CONHC_6H_4OH$
3. $C_6H_{13}CONHC_6H_4OH$
4. $C_6H_{12}CONHC_6H_4OH$
5. $C_6H_{13}CONHC_6H_4OH$
6. $C_6H_{13}CONHC_6H_4OH$
7. $C_6H_{13}CONHC_6H_4OH$
8. $C_6H_{13}CONHC_6H_4OH$
9. 50% $C_6H_{13}CONHC_6H_4OH$
   50% $C_6H_5CH_2CH_2CONHC_6H_4OH$
10. 50% $C_6H_{13}CONHC_6H_4OH$
    50% $C_6H_5CH_2CH_2CONHC_6H_4OH$

The melting points in the cases of three pairs of isomers listed in Table II as 1, 2, 3, 4, 9 and 10 might indicate that in each case they were identical substances in an impure state, but analysis and mixed melting points seem to indicate that each might be an equilibrium mixture of the two possible isomeric diacyls.

Mixed melting point of 1 and 2	38–40°
Mixed melting point of 3 and 4	37–39°
Mixed melting point of 9 and 10	50–54°

All the diacyls prepared are insoluble in water, soluble in alcohol and very soluble in ether.

SUMMARY.

A study of the diacyl derivatives of *o*-aminophenol, when one of the acyl groups was always the *n*-heptanoyl radical, has been made. The *n*-heptanoyl group was checked against the *n*-butyryl, *n*-valeryl, *n*-caproyl, phenylacetyl and hydrocinnamyl groups.

Apparently relative weight and acidity are not the controlling factors in this type of rearrangement. When complete rearrangement did occur, the nitrogen atom was shown after saponification to be attached to the heavier and less acidic group in three cases and to the lighter and less acidic group in one case. One case showed only partial rearrangement. In this case saponification products showed part of the nitrogen to be attached to the heavier and more acidic group while the remainder of the nitrogen was attached to the lighter and less acidic group.

Two monoacyls and ten diacyl derivatives of *o*-aminophenol have been prepared, isolated and studied.

Some of these compounds are being studied for antiseptic and physiological effects. The results of this investigation will be published at a later date.

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THE POTENCY OF OREGON DIGITALIS.*[1]

(A PRELIMINARY INVESTIGATION.)

BY DONALD KUO-CHIH LEE AND ERNST T. STUHR.[2]

INTRODUCTION.

The literature reveals considerable conflicting evidence relative to physiological activity of cultivated and wild growing foxglove (1, 2, 3, 4, 5, 6, 7, 8, 9) and age of the foliage (10, 11). These contradictions prompted the investigation of the native growing Oregon plants.

Foxglove grows wild throughout the Pacific slope region from Vancouver Island to California. In Oregon it is abundant along the western part of the state, but more especially in Lincoln and Coos counties.

The results here presented are from a seasonal study of wild growing Oregon digitalis, *Digitalis purpurea* L.

Procedure.—Monthly collections were made of both first- and second-year leaves during the spring and summer of 1932–1933. Tinctures were prepared in accordance with U. S. P. specifications. The fat-free preparations were placed in glass-stoppered amber-colored bottles and stored in a cool place in order to retard deterioration (12, 13, 14).

The resulting preparations were biologically assayed by the official "one-hour" frog method (15). Throughout the experiments only healthy frogs of the species *Rana pipiens* (common "grass" or "leopard" frogs) weighing 20–35 Gm. were used. Temperature was kept constant (20° C.) The degree of sensitiveness of the frogs was ascertained, using ouabain solution as a standard. Series of standardized frogs were used in assaying the respective tinctures for each particular age and month's collection of digitalis leaves.

An attempt was made to correlate physiological activity with seasonal glucosidal content by the proposed colorimetric method of Knudsen and Dresbach (16).

* An abstract based upon a thesis by Donald Kuo-Chih Lee submitted to the Graduate Faculty of the Oregon State College in partial fulfilment of the requirements for the degree of Master of Science.

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Results.—The seasonal study of wild growing digitalis revealed that the first-year leaves of the December collection were equivalent in potency to the April collection of first-year leaves.

FIRST-YEAR PLANTS.

Collections.	*Relative Potency of Preparations (Tr. Dilution 1: 5).
November	38.46
April	38.46
June	85.71

SECOND-YEAR PLANTS.

November	30.00
June	85.71
July	100.00

* Determined by comparison with ouabain as standard (Dilution—1:10,000). Apparently there is very little difference in the physiological activity of the first- and second-year plants during June.

CHEMICAL ASSAY.

A chemical determination of the active principles was attempted on the monthly samples. The method used was the colorimetric method proposed by Knudsen and Dresbach (16).

Tinctures Tested.	Readings in Mm.	Number of Mg. in a Cat Unit (17).
November:		
First-year plants	38	190
Second-year plants	42	210
December:		
First-year plants	31	155
April:		
First-year plants	33.2	166
June:		
First-year plants	24.0	120
Second-year plants	26.3	131.5
July:		
First-year plants	20.6	103
Second-year plants	22.8	110.4

Considerable difficulty was experienced due to the inability of comparing the intensity of the tinctures with the standard solution. Several attempts were made but we were not able to get any close results. The standard ouabain solution had a dark yellowish color but the tincture remains a light greenish in color, even after the addition of the neutral lead acetate solution and the alkaline picrate solution. The greenish tint of the tincture is no doubt due to the pigment (chlorophyll) of the digitalis leaves. The volume of neutral lead acetate solution called for in the method was either insufficient or the Oregon digitalis has a greater content of chlorophyll than that which Knudsen and Dresbach experimented with. As it was impossible to compare the intensity of the color of the two solutions, readings were made by attempting to measure the color tints of the two solutions.

CONCLUSIONS.

1. The physiological activity of the first-year leaves compared favorably with the second-year leaves.

2. The activity of native digitalis plants under favorable climatic conditions would probably be above U. S. P. standard.

3. One-hour frog method unsatisfactory chiefly because of the time element which has a tendency toward erratic results.

4. Observed only a slight difference in the susceptibility of frogs to cardiac stimulants through the various seasons.

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STUDIES ON THE BIOASSAY OF DIGITALIS.*[1]

III. A NEW DIURETIC OLIGURIC CAT METHOD.

BY JAMES H. DEFANDORF.

Digitalis in toxic amounts has a peripheral constrictor effect on the blood vessels of the kidney in animals (2, 8, 13, 17) which, together with its weakening effect on the circulation, results in a decreased output of urine (oliguria). Since digitalis has a cumulative action, oliguria should follow the repeated administration of small doses and the effect observed by measuring the urine output at short

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intervals. The increase in toxic activity of the drug, as shown by a constantly decreasing output of urine, should thus serve as a guide to the rate and amount of administration in intravenous methods of assay, and, by indicating the approach of death, make possible a more accurate determination of the minimum lethal dose than can be obtained by the continuous intravenous injection method of Hatcher and Brody (10, 11) and its modifications (1, 12, 19).

The cat was selected as the experimental animal because it can readily be made to exhibit diuresis. Moreover, it is the animal most used in this country for the assay of digitalis by an unofficial method.

Three tinctures of digitalis were tested, and their effects on urine output were observed following repeated intravenous administration of sub-lethal doses. The change from diuresis to oliguria was studied in its relation to the approach of death. The minimum lethal doses were determined and compared with those of the subcutaneous (15), new leg-vein (5) and new intramuscular (5) minimum lethal dose guinea-pig methods, and with systolic standstill doses of the U. S. P. X (18), modified four-hour U. S. P. X (4), Smith-McClosky intravenous (16) and Dooley-Higley intramuscular (6) frog heart methods.

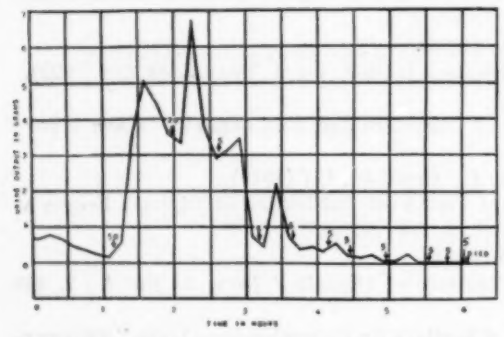

Fig. 1.—Graphic representation of urine output in the cat following intravenous administration of repeated doses of digitalis. (Cat No. 13, 10/17/33; also see protocol.)

EXPERIMENTAL PROCEDURE.

Male and female cats, ranging in weight from 1.5 to 4.3 Kg. were used. They were placed on a milk diet for about a week previous to the experiment, and in a few cases raw liver was added to the diet, but was later omitted when found to be unnecessary. The animals were weighed immediately before the experiment, and the dosages of both the anesthetic and digitalis were calculated on this basis. In some of the first experiments water was given by stomach tube immediately before administration of the anesthetic in order to insure an adequate output of urine, but this also was found to be unnecessary and was omitted in the later experiments. Sodium barbital, 0.25 to 0.3 of a gram per Kg., was given by stomach tube, and usually excellent anesthesia was obtained by the end of the hour; occasionally a few inhalations of ether were necessary in the induction of anesthesia, and at times during the course of the experiment, which usually lasted several hours.

When anesthesia was complete, the femoral vein was exposed for use in intravenous injection. A small median incision was made in the lower abdomen, exposing the bladder, and the urine removed by gentle compression or by a hypodermic syringe and needle. A small thistle tube cannula was then inserted in the bladder through a small incision, and carefully tied in so as to avoid obstructing the ureters. By means of rubber tubing this was connected with a long glass tube, and the system filled with warm saline. As fluid began to drop from the distal end of the tube it was collected in tared flasks at stated intervals, usually of ten minutes, throughout the course of the experiment, and weighed, the amount of urine excretion being plotted on graph paper.

The digitalis solution was prepared for injection by evaporating all alcohol from the tincture and diluting the residue with physiological saline to a 5 per cent solution, so that 1 cc. represented 50 mg. of the leaf. When the urine secretion reached a normal level, which on the average was about thirty minutes after cannulation of the bladder, the first injection of digitalis was made with

an accurately graded Luer tuberculin syringe into the exposed femoral vein, at the rate of 1 cc. per minute. The first dose of 50 mg. per Kg., which is about 50 per cent of the minimum lethal dose of the standard leaf for cats, has been found to be entirely satisfactory with the tinctures examined. Marked diuresis usually appeared in ten to fifteen minutes, lasting for upward of an hour (Fig. 1). When the increments of urine began to decrease, another and smaller injection of 10 to 20 mg. of digitalis per Kg. was made, and the same observations made as described above. The same procedure was repeated with successive doses of 5 mg. per Kg., until the urine excretion began to approach or fall below the normal obtained at the beginning of the experiment. This condition, which may be the result of a failing circulation or of peripheral constriction of the kidney blood vessels, or both, has proved to be a sign of approaching death. The 5-mg. doses were then injected at 10- to 20-minute intervals, and the time of death noted, cardiac stoppage being observed by mediate auscultation.

In these studies cardiac failure occurred before or simultaneously with respiratory failure, never after; artificial respiration applied in some of the earlier experiments had no beneficial effect, and was abandoned. Control injections of physiological saline, equal in liquid content to the largest amount of fluid injected with the digitalis preparations, had no effect on urinary output.

The following protocol is typical of the procedure and results obtained from the diuretic oliguric cat method (see Fig. 1).

10/17/33.	Cat, female, 2.86 Kg., on milk diet.
9:35 A.M.	Administered sodium barbital by stomach tube, 0.3 Gm. per Kg. (0.86 Gm.).
10:30	Anesthesia complete, respiration slow, deep and regular.
10:33	Began operation. Tracheotomy performed, femoral vein exposed, bladder cannulated.
10:52	Operation completed.
10:55–12:05 P.M.	Collected and weighed urine at ten-minute intervals until satisfactory control was obtained.
12:08–12:14	Injected tincture "C," 5 per cent, alcohol-free, 50 mg. per Kg., into femoral vein of right leg.
12:14–12:35	Marked diuresis.
12:30	Animal swallows, breathes rapidly and violently, alternating for several half-minute periods (nausea); heart rate markedly slowed.
12:57½–12:59½	Injected tincture "C," 20 mg. per Kg.
1:02	Marked diuresis, symptoms as at 12:30.
1:37–1:37½	Injected tincture "C," 5 mg. per Kg.; slight diuresis.
2:11–2:11½	" " " " " " " marked "
2:38–2:38½	" " " " " " " slight "
3:09½–3:10	" " " " " " " " "
3:28½–3:29	" " " " " " " " "
3:57–3:58	" " " " " " " " "
4:25	Anuria
4:30–4:31	Injected tincture "C," 5 mg. per Kg.
4:47–4:48	Injected tincture "C," 5 mg. per Kg.
4:53	Labored respiration; heart rate alternately fast and slow.
5:06–5:07	Injected tincture "C," 5 mg. per Kg.
5:07–5:11	Heart irregular; stops for a few seconds, then beats rapidly; respiration also irregular.
5:11	Heart stopped.
5:11½	Respiration ceases; no urine since 3:58.

Summary: Total mg. per Kg. of tincture "C" to produce anuria:* 100.
Total mg. per Kg. of tincture "C" to produce death: 115.

* Often anuria does not occur until death.

The average minimum lethal doses in Table I indicate that tincture "D" is 92 per cent and tincture "B" 78 per cent of the strength of tincture "C."

The minimum lethal doses for tincture "B" are exceptionally uniform, but this is not true for tinctures "C" and "D." The greatest variations from the average minimum lethal doses for "C" and "D" occurred with animals below (3, 15, 24) 2 Kg. or above 3 Kg. (4, 30).

TABLE I.—COMPARISON OF MINIMUM LETHAL DOSES OF TINCTURE "B," "C" AND "D" BY THE DIURETIC OLIGURIC CAT METHOD.

Tincture.	Cat Number.	Sex.	Weight in Kg.	Minimum Lethal Dose, Mg. per Kg.	Average Minimum Lethal Dose, Mg. per Kg.	Average Deviation.
B	17	F	2.29	80		
B	18	M	2.62	75		
B	19	F	1.54	75		
B	20	F	2.35	70	73.6	± 3.1
B	21	F	2.55	70		
B	22	M	2.20	75		
B	26	F	2.04	70		
C	3	F	1.87	62.5		
C	4	M	3.13	125		
C	6	M	2.42	85		
C	8	F	2.27	100	94.6	±15.3
C	13	F	2.86	115		
C	14	M	3.27	100		
C	15	F	1.44	80		
C	16	F	1.64	90		
D	24	F	1.84	105		
D	25	M	2.80	80		
D	27	F	2.61	80		
D	28	F	2.22	70	87.1	±15.3
D	29	F	2.76	65		
D	30	M	4.30	120		
D	31	F	2.60	90		

TABLE II.—A COMPARISON OF TINCTURES "B," "C" AND "D" BY CAT, FROG AND GUINEA-PIG METHODS.

Animal.	Method Used.	Tincture "B." Minimum Systolic* or Lethal[1] Dose in Mg. per Gm.	Tincture "C." Minimum Systolic* or Lethal[1] Dose in Mg. per Gm.	Tincture "D." Minimum Systolic* or Lethal[1] Dose in Mg. per Gm.
Frog	U. S. P. X one-hour lymph-sac	0.8	...	0.7
	Modified U. S. P. X four-hour lymph-sac	0.8	...	0.8
	Intramuscular (Dooley-Higley)	0.8	...	0.8
	Intravenous (Smith-McClosky)	0.4	...	0.4
Guinea Pig	Subcutaneous (Reed and Vanderkleed)	0.25	0.3	0.3
	New Intramuscular	...	...	0.225
	New leg-vein	0.175	0.2	0.2
Cat	New diuretic oliguric	0.074	0.095	0.087

* Frog methods.

[1] Guinea-pig and cat methods.

Table II summarizes the results of assays of tinctures "A," "B" and "C" on frogs, guinea pigs and cats. Tincture "C" was exhausted before frog assays could be made. Analysis of this table permits the following deductions:

Tinctures "B" and "D" are practically identical in activity as tested by four frog heart methods.

Tincture "B" is slightly stronger than "C" and "D" by the guinea-pig methods, "C" and "D" being of equal strength by these tests.

Tincture "B" is strongest by the diuretic oliguric cat method, whereas "C" is weaker than "D."

The results of the frog and guinea-pig methods are in closer agreement with each other than they are with those of the cat method.

When measured by the results of the intravenous frog, new intravenous guinea-pig and new diuretic oliguric cat methods, digitalis is about twice as toxic to the cat as to the guinea pig and about twice as toxic to the guinea pig as to the frog:

Cat = 1. Guinea pig = 2. Frog = 4.

DISCUSSION.

The assays reported above corroborate many observations made in the literature concerning the variations in susceptibility of cats to digitalis (7, 9, 14). The assays on tincture "B" are remarkably uniform, in contrast to the large positive and negative variations in the results obtained with tinctures "C" and "D." Large variations in susceptibility in frogs and guinea pigs are of less importance because large numbers of these animals can be used in contrast to cats, where the experimental procedure is much more prolonged, and the animals more difficult to obtain in large numbers. When small numbers of animals are used for an assay it seems logical to agree with Burn (3) that it is indefensible to set aside the results obtained from one or two cats which show a great difference from the others, such as Cats No. 3 and No. 4 in tincture "C" (Table I). Burn points out that owing to the large range in sensitivity of cats, "the average of three cats, for example, can never be assumed to be nearer the true value than that of four," and states that the average of results on a small number of cats is more nearly the true value as the number of cats is increased, the true results being obtained from the average of a very large number, such as one hundred.

In the new diuretic oliguric cat method just described the drug is not injected continuously, and this would appear to be an advantage not possessed by the intravenous methods usually employed. As digitalis is a drug which acts slowly, it would appear impossible to get an accurate determination of its true activity when employing a comparatively rapid continuous injection method.

Following the early diuretic effect, the repeated administration of small doses produces a constantly decreasing output of urine (oliguria), a condition due to toxic action, and an excellent indicator of the approach of death, more easily discernible than the heart changes ordinarily observed by auscultation in the usual cat method. Anuria occurs sometimes, before death.

It should also be observed that the best results were obtained with cats ranging in weight from 2 to 3 Kg., in the relatively small number of animals used. Cats above or below these weight limits showed a wider variation in susceptibility. These weight extremes may be identical with extremes in age which might account for the variations in resistance.

SUMMARY AND CONCLUSIONS.

A new intravenous cat method for the bioassay of digitalis is described, which utilizes the changes produced in urinary output to determine the amount and frequency of administration of the drug.

The progress from diuresis to oliguria following intravenous injection of successive doses of digitalis is a useful index of the development of toxic activity of the drug, and thus serves as a guide to the frequency and amount of its administration.

Cats showed wide individual variations in their susceptibility to digitalis, and their value in the assay of this drug appears questionable since in practice only a few animals are used.

Results of frog and guinea-pig assays agreed more closely with each other than with those of the cat method.

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THE RECTAL ABSORPTION OF DIGITALIS IN CATS.*

BY W. ARTHUR PURDUM.

INTRODUCTION.

Digitalis and its preparations, when administered by mouth, frequently cause nausea and vomiting. To overcome this untoward effect, Eichhorst, first (3), and later, other investigators have suggested administration by rectum. Therefore, digitalis preparations intended for rectal administration in suppository form and in solution have been offered to the medical profession within the last few years.

The available clinical reports on the administration of digitalis by rectum are favorable. It, therefore, seemed desirable to determine the preparation best suited for rectal use. With this objective in view, two preliminary experiments were conducted to determine whether or not digitalis is absorbed from the cat rectum. Large

* From the laboratories of A. G. DuMez, Professor of Pharmacy, and Marvin R. Thompson, Professor of Pharmacology, School of Pharmacy of the University of Maryland. Compiled from a thesis submitted to the Faculty of the Graduate School of the University of Maryland in partial fulfilment of the requirements for the degree of Master of Science.

doses of a dealcoholized fluidextract were administered and positive absorption was noted. A comparative study was then made of the rectal absorption of digitalis from different vehicles.

EXPERIMENTAL.

A fluidextract of digitalis accurately standardized as to potency was dealcoholized by evaporation at a low temperature. Two anesthetized cats were then given approximately 20 M. L. D. and 10 M. L. D. of this solution by rectum. Difficulty was encountered in keeping the digitalis solution in the rectum due to the severity of the irritation produced. However, the cats received sufficient digitalis to cause death in from 3 to $3^1/_2$ hours. These results show that digitalis is absorbed when given rectally.

For the purpose of obtaining comparative data on the rate of absorption of different preparations of digitalis when given by rectum, 5 additional series of experiments were conducted. In the first series, 5 separate experiments were carried out and in each of the remaining series, from 9 to 15 experiments. In all cases, the cats were anesthetized and kept under light anesthesia throughout the experiments by means of intraperitoneal injections of one of the barbiturates and, in some cases, ether was used as a supplement. Expulsion of the digitalis preparations was prevented by the application of anal clamps. About 5 hours after the administration of the rectal preparation, an amount of standardized digitalis solution sufficient to cause death was introduced intravenously.

SERIES NO. 1.

Suppositories were prepared, each containing the following:

Powdered Digitalis	0.3 Gm. (3 cat units)
Cacao Butter	1 Gm.

The results of the experiments with these suppositories are shown in Table I.

TABLE I.—ABSORPTION OF DIGITALIS POWDER IN CACAO BUTTER SUPPOSITORIES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs.	and Min.	Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
1	1.93	3	1.55	6	7	20.0	..	..
2	1.91	3	1.57	4	44	24.1	..	..
3	1.77	3	1.69	5	3	22.5	..	..
4	1.72	3	1.74	5	43	10.0	0.72	0.42
5	1.15	3	2.60	6	38	8.8	0.27	0.23

Since cats Nos. 1, 2 and 3 showed no absorption and cats Nos. 4 and 5 showed very slight absorption, the amount of digitalis given was increased in the next series of experiments.

SERIES NO. 2.

Each suppository used in this series contained:

Extract of Digitalis	0.375 Gm. (15 Cat units)
Cacao Butter, sufficient to make	2 Gm.

An extract of digitalis, 4 times the strength of the powdered digitalis used in the previous series, was used because the incorporation of an equivalent amount of powdered digitalis would have been impractical due to its bulk.

TABLE II.—ABSORPTION OF EXTRACT OF DIGITALIS IN CACAO BUTTER SUPPOSITORIES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.	Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
6	3.15	15	4.76	6 20	33.7	..	..
7	2.80	15	5.35	See below	..	2.80	1.00
8	2.80	15	5.35	5 50	26.5	0.15	0.05
9	2.75	15	5.45	5 53	32.5	..	..
10	2.73	15	5.49	5 6	17.2	1.01	0.37
11	2.56	15	5.85	6 10	31.6	..	..
12	2.54	15	5.90	4 12	25.2	0.02	0.01
13	2.47	15	6.07	5 19	11.0	1.37	0.55
14	2.45	15	6.12	5 47	20.6	0.39	0.16
15	2.43	15	6.17	5 24	11.6	1.27	0.52
16	2.35	15	6.38	5 10	20.3	0.32	0.14
17	2.27	15	6.60	3 38	17.2	0.55	0.24
18	2.25	15	6.66	5 56	16.7	0.58	0.26
19	1.89	15	7.93	5 27	17.0	0.19	0.10

Cat No. 7 died about 3 hours after insertion of the suppository. An autopsy revealed that the heart was in systole which is an indication of digitalis poisoning. However, the cat may have been abnormal and may have died from other causes. Cats Nos. 6, 9 and 11 showed no rectal absorption and actually required more solution intravenously than should have been needed theoretically had no digitalis been given rectally.

TABLE III.—ABSORPTION OF EXTRACT OF DIGITALIS IN GLYCERINATED GELATIN SUPPOSITORIES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.	Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
20	3.93	15	3.82	5 26	33.3	0.60	0.15
21	3.12	15	4.81	5 20	27.3	0.39	0.13
22	2.85	15	5.26	4 55	21.0	0.75	0.26
23	2.73	13.65	5.00	5 33	30.0	..	..
24	2.72	16.5	6.07	5 40	17.0	1.02	0.38
25	2.70	15	5.56	5 16	10.5	1.65	0.61
26	2.67	15	5.62	4 18	22.0	0.47	0.18
27	2.65	13.25	5.00	4 54	23.5	0.30	0.11
28	2.60	15	5.77	5 45	35.0	..	..
29	2.57	15	5.84	5 5	10.2	1.55	0.60
30	2.42	16.5	6.82	5 31	18.7	0.55	0.23
31	2.33	12.5	5.36	6 3	9.0	1.43	0.61
32	2.30	15	6.52	5 32	17.7	0.53	0.23
33	2.23	11.2	5.02	5 4	16.0	0.63	0.28
34	1.55	15	9.68	5 59	14.3	0.12	0.08

SERIES NO 3.

The base for the suppositories which were given throughout this series of experiments was Glycerinated Gelatin, U. S. P. X. Extract of Digitalis of the same lot as that employed in Series No. 2 was again used. The suppositories were prepared on two different occasions by the formulas which follow.

Lot No. 1	Extract of Digitalis	0.225 Gm. (9 cat units)
	Glycerinated Gelatin, sufficient to make	2.4 Gm.
Lot No. 2	Extract of Digitalis	0.375 Gm. (15 cat units)
	Glycerinated Gelatin, sufficient to make	2.4 Gm.

In both cases, the extract was thoroughly incorporated with the fused glycerinated gelatin after the source of heat had been removed from the base. This procedure prevented prolonged heating of the extract which would inactivate the digitalis principles.

In those cases in which the suppositories containing 9 cat units of digitalis were used, it was necessary to administer a fraction more than one suppository to approximate the dosage desired.

SERIES NO. 4.

The results obtained in the preceding experiments indicate relatively poor absorption when cacao butter or glycerinated gelatin are used as suppository bases. It was, therefore, inferred that, perhaps, the absorption was retarded by these bases. To determine the correctness of this observation, a series of experiments was run in which gelatin alone was used as the base and in which the proportion of the latter was reduced to a minimum. This was accomplished by administering No. 1 hard gelatin capsules into which 0.375 Gm. (15 cat units) of extract of digitalis was packed. Prior to insertion of the capsules, water, in an amount equal to about 10 cc., was injected into the rectum to aid the dissolution of the capsule material.

TABLE IV.—ABSORPTION OF EXTRACT OF DIGITALIS IN HARD GELATIN CAPSULES ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs.	and Min.	Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
35	3.80	15	3.95	5	4	34.9	0.31	0.08
36	3.15	15	4.76	5	13	30.7	0.08	0.03
37	3.10	15	4.84	5	17	15.0	1.51	0.52
38	3.05	15	4.92	5	21	29.6	0.09	0.03
39	3.00	15	5.00	5	33	14.9	1.51	0.50
40	2.87	15	5.23	5	47	23.0	0.57	0.20
41	2.85	15	5.26	5	38	25.8	0.27	0.09
42	2.85	15	5.26	5	20	25.0	0.35	0.12
43	2.40	15	6.25	5	0	21.6	0.24	0.10
44	2.23	15	6.73	6	21	23.3	..	..
45	2.13	15	7.04	5	39	16.3	0.50	0.23
46	1.80	15	8.33	5	19	10.5	0.75	0.42
47	1.80	15	8.33	5	7	14.5	0.35	0.19
48	1.70	15	8.82	5	46	14.0	0.30	0.18

The heart beat of cat No. 37 was weak and irregular throughout the experiment. After death, the heart was examined and found to be in diastole which throws doubt upon the probability of death from digitalis.

SERIES NO. 5.

In the experiments which follow, the possible influence of any extraneous matter was eliminated completely by injecting a dealcoholized tincture of digitalis. The tincture was prepared by the U. S. P. X method and the alcohol was removed by heating to about 50° C. in an open vessel, over which a current of warm air was passed until all of the alcohol had evaporated. The solution was injected by means of a rectal tube attached to a hypodermic syringe.

TABLE V.—ABSORPTION OF DEALCOHOLIZED TINCTURE OF DIGITALIS ADMINISTERED BY RECTUM.

Cat No.	Weight of Cat in Kg.	No. of Cat Units Given.	No. of M. L. D. Given.	Time Allowed for Absorption in Hrs. and Min.	Cc. Administered Intravenously (10 Cc. Represents 1 Cat Unit).	No. of Cat Units Absorbed.	No. of M. L. D. Absorbed.
49	3.80	19	5	5 40	14.5	2.35	0.62
50	3.35	16.75	5	5 28	35.5	..	..
51	3.30	16.5	5	5 33	31.0	0.20	0.06
52	3.02	15.1	5	4 53	19.6	1.06	0.35
53	2.85	14.25	5	4 17	19.5	0.90	0.32
54	2.38	11.9	5	5 40	6.5	1.73	0.73
55	2.35	11.75	5	See below	..	2.35	1.00
56	2.02	4.04	2	4 21	17.0	0.32	0.16
57	1.87	9.35	5	5 46	16.3	0.24	0.13

Cat No. 55 died about three hours after receiving the rectal digitalis solution. It is believed that digitalis was the cause of death because the usual symptoms of digitalis poisoning were noted.

CONTROL EXPERIMENTS.

During the course of the experiments, the problem arose as to whether or not the prolonged anesthesia and the clamping of the anus materially affected the results obtained. To solve this problem, control experiments were run as follows:

Two cats were anesthetized in the manner employed throughout this work. As soon as anesthesia was induced, the ani were clamped to simulate the conditions when digitalis was administered rectally. After about six hours, digitalis solution was introduced intravenously in an amount sufficient to kill the cats. This amount was found to be within 10% of the calculated minimum lethal dose in both cases.

DISCUSSION.

The available published clinical reports highly recommend rectal digitalis therapy (2, 3, 4, 5, 6, 7, 8 and 9), citing several advantages for it over the oral method, and suggest it as a substitute for intravenous and subcutaneous administration. The results of the investigations upon which the findings reported in this paper are based do not confirm those reported by clinicians. While it is true that in the experiments from which these results were obtained the test animals used were cats and the drug was administered under abnormal conditions, *i. e.*, prolonged anesthesia and clamping of the anus, it has been shown by control experiments that these abnormalities caused no perceptible effect on the susceptibility of the cats to the drug. It is possible, however, that the application of anal clamps may have either hastened or retarded absorption.

The absorption of digitalis from the rectum was found to be very slow and small in amount considering the large doses which were administered. Nausea and emesis occurred in the interval elapsing between the rectal administration and the intravenous administration of the drug in approximately half of the experiments. This may have been caused by the anesthetic since emesis was observed in one of the controls. The digitalis was observed to be quite irritating to the rectum since it was necessary to clamp the anus to prevent expulsion of the drug and since autopsies disclosed considerable inflammation, even in the recta of those cats on which anal clamps were not used. The rate of absorption from the rectum was also found to be irregular and inconsistent as evidenced by the large variations in the amounts which were absorbed by different cats.

Scrutiny of the preceding tables shows that digitalis is more rapidly absorbed from the rectum when administered in the form of the dealcoholized tincture than in the other forms which were employed. Following, in the order of rapidity of absorption, are glycerinated gelatin suppositories, cacao butter suppositories and finally, hard gelatin capsules.

Since available clinical results indicate rapid rectal absorption, it is evident that either the procedure of study which has been followed does not reflect accurately the absorption in the human, or, it is possible that the means by which other workers made their observations are not sufficiently dependable. Whether or not the procedure used in this work reflects the absorption rate in humans, it is believed that a comparative study of rectal, oral and subcutaneous absorption using this technique, will provide reliable information on the relative absorption rate through the above three avenues of administration in humans. However, future work is contemplated to compare relatively these three means of administration.

In view of the foregoing work, it appears that the rectal mode of giving digitalis may be a good one when digitalization is to be maintained over a rather lengthy period and when a prompt action is not essential.

CONCLUSIONS.

1. Digitalis is absorbed from the rectum.
2. The rectal absorption in cats is very slow, irregular and erratic.
3. Considerable irritation and inflammation was found to be produced in the rectum as a result of rectal administration of digitalis.
4. The most rapid absorption by rectum was observed when a dealcoholized tincture of digitalis was given.
5. The actual significance of these results will not become evident until the absorption rate following oral administration has been determined in the same manner.
6. The rectal method for administering digitalis should be subjected to more investigation before it be accepted as conventional.

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NON-HEPTANE CONSTITUENTS OF DIGGER PINE (PINUS SABINANA).

BY ARTHUR H. UHL.*

In 1928, Foote (1), in coöperation with the Ethyl Gasolene Corporation of Yonkers, N. Y., rectified the principal constituent of Jeffrey Pine oil, heptane. The non-heptane constituents of the oil were further investigated. This investigation revealed the presence of *n*-octylic, *n*-nonylic and *n*-decylic aldehydes.

Approximately 20 gallons of that portion of the oil of digger pine which boils above 110° was received from the California Chemical Corporation. The heptane which constitutes approximately 90–93 per cent (2) of the oil had been previously removed. The 20 gallons, therefore, represented between 1800 and 1900 gallons of the original oil.

Isolation of the Aldehydes.—The aldehydes were removed from the oil by shaking with a 30% solution of sodium acid sulphite. The solid addition product was separated on a force filter and washed with ether. The aldehydes were regenerated by treatment with sodium carbonate and separated by steam distillation. There resulted 625 Gm. of aldehydes. The aqueous sulphite mother liquor was treated likewise and an additional 51 Gm. were obtained.

Identification of the Aldehydes.—Because excess heating was likely to destroy or change some of the higher aldehydes, the first fractionation was run as rapidly as possible. The 625 Gm. of aldehydes were fractionated, under a pressure of 3 mm., into ten convenient fractions using a short Vigreaux column.

	B. P.	Sp. Gr.
1	– 45°	0.8182
2	45– 50°	0.8236
3	50– 60°	0.8260
4	60– 70°	0.8281
5	70– 80°	0.8400
6	80– 90°	0.8560
7	90–100°	0.8563
8	100–110°	0.8501
9	110–120°	0.8520
10	120–130°	0.8495
11	Residue	

Inasmuch as decomposition took place in Fractions 9 and 10, distillation was discontinued.

Although the fractions obtained gave some indication as to the possible aldehydes present, the melting points of derivatives were inconsistent and not sharp. The individual fractions were refractionated under a pressure of 10 mm. using a 12-inch Widmer column.

The various fractions yielded:

Fraction No. 1.		Fraction No. 4.	
a	–56°	*a*	74–76°
b	56–58°	*b*	76–78°
c	58–60°	*c*	78–80°
d	Residue	*d*	Residue

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Fraction No. 2.

a 60–62°
b 62–64°
c 64–66°
d Residue

Fraction No. 3.

a 66–68°
b 68–70°
c 70–74°
d Residue

Fraction No. 5.

a 84–86°
b 86–88°
c 88–90°
d Residue

Fraction No. 6.

a 90–92°
b 92–94°
c 94–98°
d Residue

Fraction No. 7.

Decomposition began and distillation was discontinued.

By way of comparison, the constants of the aldehydes and derivatives of previous workers may be tabulated with those found.

FRACTION No. 2.

	Found.	Recorded for *n*-Octyl Aldehyde.
B. p.	60–62°	60–63° at 10 mm. (3)
Sp. Gr.	0.8236 at 20°	0.8211 at 20° (3)
n_D	1.4206 at 20°	1.4955 (4)
α_D	±0	±0 (4)
M. p. of thiosemicarbazone	94–94.5°	94–95° (5)

This fraction corresponds to *n*-octyl aldehyde.

FRACTION No. 3.

	Found.	Recorded for *n*-Nonylic Aldehyde.
B. p.	70–74° at 10 mm.	72° at 10 mm. (6)
Sp. Gr.	0.8297 at 20°	0.8277 at 15° (7)
n_D	1.4273 at 20°	1.42452 at 16° (7)
α_D	±0°	±0° (7)
M. p. of thiosemicarbazone	77°	77° (5)

This fraction corresponds to *n*-nonyl aldehyde.

FRACTION No. 6.

	Found.	Recorded for *n*-Decyl Aldehyde.
B. p.	90–92° at 10 mm.	92° at 10 mm. (8)
Sp. Gr.	0.8502 at 20°	0.8538 at 15° (9)
n_D	1.4287 at 20°	1.4273 (9)
α_D	±0°	±0° (9)
M. p. of thiosemicarbazone	99–100°	99–100° (5)

This fraction corresponds to *n*-decyl aldehyde.

On standing in a refrigerator, Fractions 7, 8 and 9 became partly solid. The solid white material was collected on a force filter, recrystallized from alcohol and dried. It had a melting point of 42° to 43°. After further purification by recrystallization from alcohol the melting point remained unchanged.

Lauric Aldehyde.	Found.	Recorded.
M. p.	42–43°	44.5° (10)
M. p. thiosemicarbazone	100–100.5°	101.5–102.5° (11)

This fraction corresponds closely to lauric aldehyde which is indicated.

The mother liquor was placed in a refrigerator and again solid material separated which partly liquefied when an attempt was made to collect it at room temperature. The solidifying point was determined and found to be 22.5°.

Myristic Aldehyde.	Found.	Recorded.
M. p.	22.5°	23° (12)
M. p. oxime	82.5–83.5°	82.5° (12)
M. p. semicarbazone	101.5°	100–101° (13)
		106° (12)

This fraction corresponds to myristic aldehyde.

There are indications of other aldehydes present, especially those with a larger number of carbon atoms, but it was impossible to obtain derivatives pure enough to characterize the compounds.

CONCLUSION.

N-octylic, *n*-nonylic, *n*-decylic and *n*-myristic aldehydes have been isolated and identified and *n*-lauric aldehyde is indicated.

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RUSSIAN ERGOT.

BY H. H. RUSBY.

No specific account of Russian ergot, cured as our Pharmacopœia directs, and preserved in its natural state, has come to my attention. All published information that I have seen has related to commercial supplies, which have been accurately described by Henning as "usually arriving in a damp and moldy condition."

More than a year ago, I entered into communication with the Russian department of agriculture for the procural of samples officially prepared and sent direct, so as to arrive in an unaltered state. I made it clear that my criticisms of Russian ergot had no relation to Russia or its products as such, but had been made wholly in the interest of improvement of the materia medica. Several years ago, I had urged our food and drug authorities to secure, through our State Department, cooperation with Russia in the investigation of this subject and in the improvement of the latter's product, but without result. The Committee of Revision has taken no steps, as a part of their research work, to ascertain the facts regarding this drug. Thus I, perforce, took it up myself.

In the spring of 1934 I received official assurance that during the coming harvest the desired samples would be prepared and sent to me, and in the Fall the following collections were received:

No. 1. Collected at Verhovski, Central Russia District, Select Experiment Station, August 1934.

No. 2. Collected at Gorkey Province, formerly Nijniy, Novgorod, Plant Protection Institute, August 14, 1934.

No. 3. Collected at West Russia Minsk Agricultural Experiment Station, August 19, 1934.

No. 4. Collected at West Russia (Belorussia), Minsk Agricultural Station, August 20, 1934.

No. 5. Collected at Central Russia, Voronej Agricultural Experiment Station, August 1934.

No. 6*a*. Collected at Ucraine, Kalirkov Province, from a barn in the survey District, August 1934.

No. 6*b*. Obtained from a grain elevator in the same place.

No. 0. Collected in Central Russia, Black Earth Province, Semilovski District, Moroneji Station for Plants, August 1934.

Later, a second shipment was received, containing the following samples:

From East Siberia Select Center, Voronej District, September 8, 1934.
From southeast Russia, Saratov Region.
Two others, locality not specified.

The differences observed among these samples were of minor importance and insignificant, the important questions relating to their agreement with or disagreement from Spanish ergot, and the Russian ergot that has been known in the American market. The most important of these questions related to the color of the fractured surface. That of Spanish ergot is characteristically white. That required by our Pharmacopœia is "white, tinged with pink or gray" (see ergot monograph, published by the Revision Committee, September 1, 1934). The most careful examination of the official and authentic samples here considered fails to show any grains having a "pink" or any other than a white fracture! Since these samples represent all the important collecting districts of Russia, the conclusion is inevitable that normal Russian ergot exhibits only a white fracture.

This naturally raises a question as to why the Committee of Revision should have specified the pink fracture, irrespective of its source. This must be because the Committee has depended for its description on the color ordinarily presented by the Russian ergot that has been admitted to use in this country, and which has been pink or purplish. As a matter of fact, it is known to every one that practically all the Russian ergot that has been in use in the United States until recently has shown this purplish fracture and has therefore been at disagreement with the normal product, as now shown by the samples under consideration. This in turn must be due to the fact that these supplies have undergone a color change as a result of the "damp and moldy" conditions to which they have been subjected.

In order to verify this conclusion, I made a mixture of portions of all the samples, soaked them thoroughly in water and permitted them to lie in a warm place until badly decomposed, whereupon they were found to have the "pink" or purplish color on fracture.

We have, however, a somewhat more practical evidence of this fact. It is a fact that our food and drug officials, as a result of the famous ergot controversy of the past few years, have discontinued the admission of the damaged ergot with pink fracture referred to, so that, at the present time, we find the Russian ergot of our market of good quality and presenting the same white fracture and characteristic odor as that of the official samples here considered.

A very remarkable situation is thus presented. The Committee of Revision, basing its action on a knowledge of the adulterated article formerly common in our market, specifies the pink fracture of that product, but the food and drug officials correct their former practice, excluding the adulterated article, and by doing so, directly violate the present Pharmacopœia requirement! What can be done to harmonize the existing contradiction? Two alternatives are presented. The Pharmacopœia Committee may correct its description, or the food and drug officials may resume their former custom, in order to conform with the Pharmacopœia. The only other possible course would be to subject all sound Russian ergot to a process of soaking and fermentation, in order to develop the required pink color.

An interesting question is how the Russian ergot of commerce came to be changed from its natural state so as to acquire the purplish color. At present, this can only be conjectured, but it is my personal opinion that somewhere on its way from production to importation, it has been moistened in order to increase its weight, the resulting decomposition having then occurred.

Aside from the matter of fracture-color and odor, this official ergot shows little difference from the well-known sound product of Spain and Portugal. Indeed, there is no good reason why this difference in fracture-color should exist between individuals of the same plant species as grown in two countries. The grains have the same clear, bright outer surface and characteristic odor as the Spanish article. Externally, the color is not such a dark chocolate as that of the Spanish. It might, perhaps, be better described as of a dull black, ranging toward gray-black, and with a slightly reddish tinge when viewed in a strong light. Number 6 is almost black; Nos. 1 and 4 almost equally so; Nos. 2 and 3 almost as dark, and both show a little more of the reddish tinge mentioned. Numbers 5 and 0 show the grayish tinge mentioned.

In form, the grains do not differ greatly from the Spanish, although in general a little more slender and smaller. The following table shows the sizes:

No.	Average Length.	Thickness.
1	1.6 cm.	3 to 5 mm.
2	1.3 cm.	2 to 4 mm.
3	1.6 cm.	2.5 to 6 mm.
4	1.6 cm.	3 to 5 mm.
5	1.3 cm.	2 to 3 mm.
6	1.4 cm.	2.5 to 4 mm.
0	1.1 cm.	1.5 to 3 mm.

NOTE: Harry Taub, Assistant Professor in my Department, in collaboration with Abraham Taub, Assistant Professor in the Department of Chemistry, performed a series of chemical assays on the fluidextracts of Russian ergot and Spanish ergot referred to in this article, and found that there is practically no difference between the two ergots when the fluidextracts are made from a good quality crude drug. Their assays showed an average of 0.64 mg. of ergotoxine ethanesulphonate per 100 cc. of fluidextract of Russian ergot and 0.65 mg. per 100 cc. of fluidextract of Spanish ergot.—H. H. R.

A very striking difference is found between the Spanish and normal Russian ergots after being powdered, the Russian powder being blackish, the Spanish light brown and with a strong pinkish tinge.

The following conclusions are clearly established by the evidence here given:

1. The normal fracture color of all ergot is white.
2. The purple fracture color that has been commonly seen in Russian ergot is the result of decomposition caused by exposure to dampness and resulting putridity.
3. The specification by the U. S. P. Revision Committee of pink color in the fracture of ergot is the result of the former prevalence in our drug market of such decomposed ergot.
4. At the present time, the Russian ergot in the American market is in general of sound quality and exhibits a white fracture color.
5. All reference to pink fracture should be eliminated from the U. S. P. description of ergot.
6. Whatever method of bio-assay may be adopted should be based on tests made with ergot of white fracture. Tests that have been made with the deteriorated ergot of pink fracture should be scrapped.

All the specimens of Russian ergot herein referred to are preserved in the museum of the New York College of Pharmacy, where they may be seen.

That portion of the same samples that has been caused to develop the purple fracture color by decomposition is also preserved at the same place.

A sample of Russian ergot, such as is now being sold in the New York market, of sound quality and exhibiting a white fracture, will also be found there.

Portions of all the above samples have been submitted and deposited with this paper.

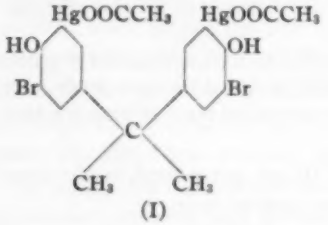
To anyone who still retains enough interest in the cockscomb test to apply the same, samples of the fluidextract made from these sound Russian ergots and from similar sound Spanish ergot, will be supplied upon request.

A bill rendered by the Pharmacy of J. B. Caventou for "La Dame aux Camelias." Without giving the titles, we are assuming the items to be: A bottle of "Sedlitz water," Cucumber Pomade, Syrup of Acacia, Narbonne Mixture, Potassium Sulphate solution, a bottle of Sulphur Water (Boréges), Sulphur Cerate, a bottle of Sedlitz Water, Acacia, Spermaceti.

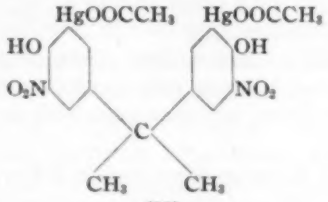
STUDY OF GERMICIDAL AND ANTISEPTIC ACTIVITY OF SOME MERCURY COMPOUNDS.*,[1]

BY E. MONESS, S. E. HARRIS AND W. G. CHRISTIANSEN.

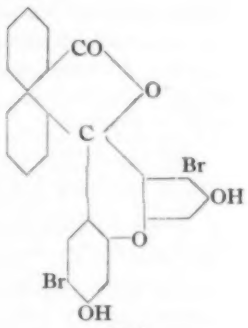
Three compounds were selected for this study, 3,3′-dibromo-4-4′-dihydroxy 5-5′-diacetoxymercuri diphenyl dimethyl methane (I); 3,3′-dinitro-4-4′-dihydroxy-5-5′-diacetoxy-mercuri-diphenyl-dimethyl-methane (II); and a mono-acetoxy-mercuri-derivative of 5′,5″-dibromo-resorcinol diphenein (III). The position



(I)



(II)



(III)

of the mercury in the product (which will be designated as (IV)) obtained from (III) was not determined. Mercurated dibromo-fluorescein is believed to be mercurated in one of the resorcinol nuclei. However, recent studies in this laboratory on mercurated dibromo-diphenyl-phenol-phthaleins (1) and mercurated derivatives of substituted diphenol-isatin (2) strongly suggest that this type of compound may mercurate in the phthalic acid, diphenic acid or corresponding portions of the molecule.

The three compounds all showed useful germicidal activity:

TABLE I.—TESTED IN DISTILLED WATER.

Compound.	Dilution Killing. Typhoid. 5 Min.	Dilution Killing. Typhoid. 10 Min.	Dilution Killing. Staphylococcus Aureus. 5 Min.	Dilution Killing. Staphylococcus Aureus. 10 Min.
(I)	1–1500	1–1500	1–1500	1–2500
(II)	1–1000	1–1500*	1–5000	1–5000
(IV) *a* 1st batch	1–250	1–2000	1–500	1–1000
b 2nd batch	1–1000	1–4000	1–500	1–1000

* Inhibits growth only—does not kill.

TABLE II.—TESTED IN BLOOD SERUM.

Compound.	Dilution Killing. Typhoid. 5 Min.	Dilution Killing. Typhoid. 10 Min.	Dilution Killing. Staphylococcus Aureus. 5 Min.	Dilution Killing. Staphylococcus Aureus. 10 Min.
(I)	1–500	1–500	1–1000	1–1500
(II)	*Not Tested.*			

* Section on Practical Pharmacy and Dispensing, Madison meeting, 1933.

[1] Research Department of the Chemical and Pharmaceutical Laboratories, E. R. Squibb and Sons, Brooklyn, N. Y.

(IV)	*a*	1st batch	1–100	1–1000	1–250	1–500
	b	2nd batch	1–250	1–1000	1–100	1–500

Compound (IV) was further tested for bacteriostatic activity.

Batch.	Dilution at Which Compound Is Bacteriostatic. Typhoid.		Staphylococcus.	
	24 Hrs.	48 Hrs.	24 Hrs.	48 Hrs.
1	1–20,000	1–10,000	1–30,000	1–20,000
2	1–100,000	1–50,000	1–500,000	1–250,000

The examination also included tests of the action of compounds (I) and (IV) on tissue, with the following results:

Compound I.—1. Non-irritating to shaved unabraded skin and to shaved abraded skin. 2. Produces slight to moderate swelling in subcutaneous tissue on repeated injection persisting for 21–24 days. 3. Autopsies following injection showed no degenerative changes due to the toxicity of the compound in liver or kidney. The autopsies were performed at the end of the test, so that no information was furnished as to possible temporary toxic action.

Compound IV.—1. Non-irritating to shaved and unabraded skin. 2. Only slightly irritating to shaved abraded skin. 3. Produces very slight swelling on subcutaneous injection and a scab at the site of intradermal injection.

Solutions Used in Tests.—The compound (IV) was prepared for test by dissolving in water containing 2 molecular equivalents of sodium hydroxide and diluting to a final concentration of 2%. This solution was diluted with distilled water immediately prior to the germicidal and bacteriostatic tests. The same solution was used in the animal experiments.

Solution of Compound (I) was effected in an exactly similar manner, except that the original concentration was 1–500. Compound (II), however, required a large excess (about 15 mols.) NaOH to produce a clear 1–250 or 1–500 solution. The latter concentration was used for testing.

The animal experiments were conducted on albino rats.

EXPERIMENTAL.

The preparation of these compounds was carried out along familiar lines, mercuration of the suitable intermediates being effected in boiling alcohol solution.

Resorcinol Diphenein.—The diphenein required for compound (IV) was prepared by the procedure of Dutt (3). The starting material was technical 70% phenanthrene which was oxidized to phenanthraquinone by the method of Oyster and Adkins (4), and subsequently to diphenic acid according to German Patent 516,282, using sodium peroxide as the oxidizing agent. Diphenic anhydride was then prepared by the method of Oyster and Adkins (5) and condensed with resorcinol (3). The product, however, did not melt at 172° C. as stated by Dutt, but softened at 70° C. and is completely melted at 100° C. The bromine derivative, however, was prepared without difficulty.

Dibromo-Resorcinol-Diphenein.—Thirty-five cc. of a 20% solution of bromine in glacial acetic acid was added to a well-stirred solution of 8.6 Gm. of resorcinol diphenein in 170 cc. glacial acetic acid. The mixture was heated on the steam-bath for fifteen minutes and poured into 2000 cc. of cold water. The yellow flocculent precipitate was filtered off, washed with water and dried, giving a yellow powder.

0.2277 Gm. of substance required 7.92 cc. of $N/10$ $AgNO_3$ solution.

Br found, 27.83%.
Calculated for $C_{28}H_{14}O_5Br_2$, 28.26%.

Mercuration of Dibromo-Resorcinol-Diphenein.—Fifteen Gm. of dibromo-resorcinol-diphenein was dissolved in 250 cc. of alcohol and the solution refluxed with good stirring. A solution of 8.41 Gm. of mercuric acetate in 42 cc. of water slightly acidified with acetic acid was then added dropwise during 45 minutes to the well-stirred, boiling diphenein solution. After boiling and stirring for a further period of 15 minutes a brown precipitate had formed and the clear superna-

tant liquid gave a negative test for inorganic mercury with ammonium sulphide and sodium hydroxide. The precipitate was filtered off, washed with alcohol and dried *in vacuo*. Yield—16 Gm. The substance was a brownish purple powder insoluble in the common organic solvents but readily soluble in alkali hydroxide solutions. Such solutions were dark red by transmitted light, opaque with a greenish fluorescence by reflected light, and did not stain the skin.

0.2523 Gm. of sample gave 0.0728 Gm. of mercury.
Hg found, 28.80%.
Calculated for $C_{28}H_{16}O_6Br_2Hg$, 24.22%.

The high mercury content indicates contamination with the diacetoxy mercuri compound or hydrolysis to the hydroxymercuri derivative. This point was not investigated since the use of the compound in aqueous alkaline solutions inevitably transforms any acetoxy derivative to the hydroxy form.

4,4'-Dihydroxy-Diphenyl-Dimethyl-Methane.—One hundred and eighty-eight Gm. phenol, 30 Gm. acetone and 15 Gm. phosphorus oxychloride were mixed at 20° C. The temperature was then raised to 40–45° C. and a further 15 Gm. phosphorus oxychloride added. The mixture was allowed to stand for 72 hours during which time it set to a solid mass. This was broken up, treated with water and steam distilled to remove excess phenol. The residue was cooled with vigorous stirring. The granular product was filtered off, washed with water, dried and purified by distillation *in vacuo*.

B. p., 225–230° C./4 mm. M. p., 144° C.
Yield—119 Gm.
0.2297 Gm. gave CO_2 0.6627 Gm.; H_2O 0.1458 Gm.

	Carbon.	Hydrogen.
Found Found	78.7%	7.11%
Calculated for $C_{15}H_{16}O_2$	78.9%	7.06%

3,3'-Dinitro-4,4'-Dihydroxy-Diphenyl-Dimethyl-Methane.—Thirty-one Gm. of 4,4'-dihydroxy-diphenyl-dimethyl-methane was dissolved in 300 cc. glacial acetic acid and to the well-stirred solution 14 Gm. concentrated nitric acid was added dropwise. After standing twenty minutes the reaction mixture was poured into 1500 cc. of cold water. The gummy precipitate was washed with cold water and recrystallized from 250-cc. absolute alcohol. It formed a yellow micro crystalline powder.

M. p., 132° C.
0.3115 Gm. gave 23.5 cc. moist N_2 at 24° C. and 767 mm.
N found, 8.5%.
Calculated for $C_{15}H_{10}N_2O_6$, 8.9%.

3,3'-Dinitro-4,4'-Dihydroxy-5,5'-Diacetoxy-Mercuri-Diphenyl-Dimethyl-Methane.—10.5 Gm. of 3,3'-dinitro-4,4'-dihydroxy-diphenyl-dimethyl-methane was dissolved in 250 cc. of alcohol and the solution stirred under a reflux condenser. A solution of 19 Gm. of mercuric acetate in 100 cc. water and 5 cc. glacial acetic acid was then added and the mixture refluxed and stirred for 18 hours, until a side test showed absence of ionic mercury. The precipitate was then filtered off, washed with alcohol and ether and dried. The product formed a bright yellow powder insoluble in alcohol and the common organic solvents but soluble in alkali hydroxide solutions to yield fluorescent brown solutions.

Yield, 17.0 Gm.
0.1995 Gm. gave 0.0948 Gm. Hg.
Hg found, 47.5%.
Calculated for $C_{19}H_{18}N_2O_{10}Hg_2$, 48.1%.

3,3'-Dibromo-4,4'-Dihydroxy-5,5'-Diacetoxy-Mercuri-Diphenyl-Dimethyl-Methane.—28 Gm. 4,4'-dihydroxy-diphenyl-methane was dissolved in 250 cc. glacial acetic acid and 40 Gm. bromine added dropwise with good stirring. The solution was then allowed to stand fifteen minutes and

poured into 1500 cc. of water. The sticky precipitate was washed free of acid with water and mercurated without further purification, because attempts to crystallize this substance led to decomposition with the formation of red coloring matters.

The hot solution of 23 Gm. mercuric acetate in 100 cc. of water and 5 cc. glacial acetic acid was added to a refluxing solution of 11 Gm. crude 3,3′-dibromo-4,4′-dihydroxydiphenyl-dimethylmethane with continuous stirring. About fifteen minutes were required for the addition of the mercuric acetate solution. A white precipitate commenced to form during the addition of the mercuric acetate and continued for about 45 minutes. At the end of this time inorganic mercury could no longer be detected in the solution. The latter was cooled and the heavy white precipitate collected by filtration, washed with ether and dried.

Yield, 18 Gm.
M. p.—decomposes 250° C.
0.1704 Gm. gave 0.0775 Gm. Hg.
Hg found, 44.5%.
Calculated for $C_{19}H_{18}O_6Br_2Hg_2$, 44.5%.

The product formed a white amorphous powder, insoluble in the common organic solvents but soluble in a considerable excess of alkali hydroxide solution.

The mercury analyses reported here were carried out by the Whitmore gold crucible method.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

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VEGETABLE EXTRACTS AND BLOOD-SUGAR.*

BY PAUL S. JORGENSEN AND E. V. LYNN.

Just after the discovery of insulin Collip (1) prepared from various vegetables, as well as from animal tissue, extracts which were capable of producing hypoglycemia in animals. The effects differed from those by insulin in requiring a comparatively long period before their appearance. A further very interesting observation he made was that the serum or defibrinated blood of an animal, made hypoglycemic by insulin, by the plant extracts, by chemicals, by starvation or by pancreatectomy, had similar marked lowering effect on the sugar in another animal and could even cause death. The decrease in sugar and toxicity could thus be transmitted from one individual to another, apparently without limit.

Thalkimer and Perry (2), in a very limited study, reported an insulin-like action by injection of raw potato juice. Winter and Smith (3) noted similar results from extracts of yeast. Others (4) have partly confirmed or directly contradicted this testimony.

In 1927 Allen (5) described the action of myrtomel (earlier called myrtillin), an extract made from leaves of the genus *Vaccinium* by a process similar to that for

* Seattle, Washington, June 20, 1934.

isolating insulin. It had no effect on the sugar in normal, fasting animals but reduced or completely suppressed the hyperglycemia following the administration of large quantities of dextrose to dogs and men and diminished the glycemia and glycosuria from epinephrine. The most striking characteristic was an apparent storage, since the effects lasted several weeks after a single dose of 1 Gm. Larger amounts did not increase this effect and were entirely non-toxic, as was also continual administration over long periods. Furthermore, the blood-sugar of totally depancreatized dogs was stabilized by ingestion of myrtomel and the span of life was increased four to five weeks.

Clinical experience, which was at that time much less striking, has not been particularly encouraging. Of 81 diabetic patients, Allen found that 36 were benefited and in 6 it was possible to stop the use of insulin entirely (18 to 54 units daily). More recently he came to the conclusion that there is no definite insulin-replacing effect. Myrtomel was afterward placed on the market for experimental purposes, but its subsequent withdrawal and abandonment would seem to indicate that others could not get satisfactory results in diabetes.

Others have attributed similar properties to extracts of various plants: grapefruit by Taylor and Atter (6), later refuted (7); fragrant sumac and bugleweed (8); alfalfa, clover, corn silk, etc. (9); species of *Vinca* (10). Poole, in an unpublished work here, found similar results from extracts of *Gaultheria shallon* (salal), of *Vaccinium ovatum* and of *V. parvifolium*.

We started the present investigation to determine the nature of the substance responsible for this power to reduce the amount of sugar in the blood.

EXPERIMENTAL.

Rabbits, which were used as test animals, were kept on a standard diet, which was satisfactorily adequate, and under conditions as nearly ideal as possible. The withdrawal of blood for analysis was made at fixed times of day and under equal conditions otherwise.

After a large number of trials, it was found that the normal amount of sugar in the blood could be placed approximately at 0.109 ± 0.009 per cent, using the Shaffer-Hartmann method of determination (11). In a similar series of experiments it was found that 0.5 mg. of epinephrine gave about 0.176 per cent sugar in 90 minutes and 0.196 in 120 minutes, while 1 mg. of epinephrine gave 0.278 and 0.294 per cent, respectively, in the same times.

An extract was made from the leaves of salal by Allen's method and fed to rabbits in a dose of 1 Gm. daily (equivalent to 50 Gm. of leaves) for several days. No effect could be observed on the level of blood-sugar nor on epinephrine hyperglycemia which was produced every day during the experiment. Subcutaneous injections of the extract, equivalent to 60 Gm. of the leaves, were likewise without effect, as were also injections of fractions made by dialysis and of aqueous and alcoholic extracts of the leaves. In no case could active material be found.

Similar negative results were found with *Vaccinium ovatum*. In no instance could any extract or fraction be found to alter the normal level of blood-sugar or that after action of epinephrine. We are convinced after hundreds of experiments that the solutions made in various ways have no power to reduce the amount of sugar.

In view of the circumstances it seemed advisable to repeat some of the work on myrtomel. Allen (5) described preparations from two species of *Vaccinium*, but the myrtomel later used by experimenters came from an unknown source and according to the manufacturers, the species used is immaterial. Consequently, a sample of leaves from *V. dumosum* was obtained from near Sudbury, Massachusetts, extracted and tested on rabbits. Again results were entirely negative, since orally or by injections no effect on blood-sugar, either normal or after epinephrine, could be obtained by amounts equal to 50 Gm. of leaves.

At this stage the problem began to take on a different light and we were forced to consider

it from the negative viewpoint. Possibly such preparations from plants do not have an effect on sugar metabolism, in spite of reports to the contrary. With this in mind, it was decided to repeat the earlier work of Collip (1).

An alcoholic extract was made from green onion tops and concentrated according to his method. This was injected daily as before in amount equal to 20 Gm. of original material. There was made also an aqueous extract from the onion tops and injected in the same amount. Although many such tests were performed, we could never note any change in the normal amount of sugar nor in the level after injection of epinephrine.

Exactly similar results were obtained with fresh lettuce leaves (25 Gm. daily) and with fresh cabbage leaves (20 Gm. daily). In all cases the methods of preparing the extracts were according to Collip.

In order to make the matter still more convincing, we tested some of these preparations on a depancreatized dog. The animal lived for more than five days, during which time there were injected at various periods extracts equivalent to 100 Gm. of huckleberry leaves, to 100 Gm. of salal leaves and to 60 Gm. of fresh lettuce leaves. In no case was the curve of blood-sugar altered. Insulin was capable of lowering the amount of sugar but could not prevent death in coma on the sixth day.

The interesting observation by Collip that hypoglycemia could be transmitted from one animal to another next engaged our attention. He found that, if a rabbit was rendered low in blood-sugar by insulin, by plant extracts, by guanidine derivatives or by starvation, injection of its serum or defibrinated blood would confer a similar condition on a second animal.

An attempt was made to confirm this for insulin. A rabbit, given 20 units of the latter by injection, was in a state of violent convulsions three hours later. While in this condition it was bled and the blood was defibrinated by whipping. A second rabbit was injected with 10 cc. of this product and then observed for more than a week. The amount of sugar in the blood was normal at all times and it exhibited no unusual symptoms. Several repetitions of this experiment gave the same result.

DISCUSSION.

From a study of the results herein contained and those of previous experimenters, we are forced to conclude that the reputed therapeutic value of plant extracts in the control of sugar is erroneous.

Collip's work may be criticized from the standpoint of the quantity of liquid injected and of the five days of starvation. He reports the injection of 50 to 90 cc., which would probably dilute the blood considerably and also cause a shock to derange the general metabolism. Furthermore, he observed a reduction in sugar in the case of some extracts but was often unable to get a similar result with the same materials in other animals. It appears that the effects obtained were due to the condition of the subject rather than to a specific constituent of the extract. If there was such a constituent, consistent results should be obtained. In the earlier work on insulin an active extract invariably exerted its effect on all animals within six hours. Some of Collip's extracts did not develop a subnormal blood-sugar until five days after injection and, since food was withheld entirely during the course of the experiment, it is obvious that the reduction in sugar was due to starvation.

Thalkimer and Perry (2) noted from 5 cc. of raw potato juice intravenously a reduction of sugar from 0.17 down to 0.13 per cent. They did not state the method of determination but it is evidently one capable of considerable error, or the amount found for normal would not be so high. One experiment only was reported and it would seem inadvisable to draw any exact conclusion therefrom.

Winter and Smith (3) used extracts of yeast from various sources. Of 17 experiments reported, only 3 showed lower than normal amount of blood-sugar and an attempt to repeat one of these resulted in failure.

In view of these facts, our own experiments and a careful survey of other literature, it seems to us entirely reasonable to question the existence of any evidence that plants contain a substance which will alter amounts of sugar in the blood.

SUMMARY.

No evidence could be found for the reputed activity of plant extracts in reducing normal or high blood-sugar. Also no evidence could be found for any transference of hypoglycemia from one animal to another.

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SUGGESTIONS FOR THE IMPROVEMENT OF PROFESSIONAL RELATIONS BETWEEN DENTISTS AND PHARMACISTS.*

BY C. L. WHITMAN, D.D.S.

The professions of Dentistry and Pharmacy have been very closely related since their beginning. It is my purpose to point out some of the reasons for and method by which the pharmacists and dentists may coöperate to their mutual advantage.

In the United States there are about 67,000 dentists, all of whom prescribe drugs to a certain extent. But as a rule, while drugs are used often they are not prescribed as effectively or skilfully as they might be. I do not mean to condemn the dental profession as a whole, but this condition exists more frequently than it should. Dentistry has been practised for centuries but not as we know it to-day; modern dentistry, as a distinct and separate profession, was born in 1839 when the Baltimore College of Dental Surgery, the first dental school in the world, was established in Baltimore. Dentistry and medicine were from that year practically divorced and while dentistry, in its early days, depended largely on medicine for its development, its fundamental studies are at present based on biology, exactly as is medicine or any other branch of the healing art. Before this first dental college was established few specific books on dental therapeutics existed; the little knowledge concerning the action of drugs was scattered through the few dental works which existed at that time, or was closely guarded by its possessors. Since then dentistry has rapidly forged ahead—great strides have been made and dentistry is continuing to progress.

* Section on Education and Legislation, A. PH. A., Washington meeting, 1934.

As the profession of dentistry has advanced and become more of a factor in the healing art, it has been increasingly exploited by many unscrupulous manufacturers; preparations, concerning which little or nothing is stated as to their formulas, are being constantly brought to the dentist's attention. This condition, I believe, is in a great measure unconsciously encouraged by the dentist because much of his prescribing is done by word of mouth. This is due in part to inadequate training in this particular subject in the dental schools and by the constant pressure upon the dentist through detail men and the advertising of preparations concerning which little or nothing concerning their make-up is stated. The American Dental Association is not unaware of this condition and accordingly it has established a Council on Dental Therapeutics. The purpose of this Council is to acquaint the profession with preparations and drugs which are of use to dentistry and also to expose those preparations which are useless or unacceptable. The results of their findings are reported each month in the *Journal of the American Dental Association*. These findings will be compiled in a book similar to the N. N. R. of the American Medical Association and represent a great forward stride in dental therapeutics.

One of the ways in which pharmacy and dentistry can work together is through personal contact of individuals of both professions. The pharmacists who are conducting the pharmacies may suggest to dentists with whom they are acquainted ways in which they may prescribe drugs to better advantage. Dentists, on the whole, are eager for information; to cite a concrete example of just what I mean—let us take sodium perborate, which is one of the drugs a dentist might wish to prescribe. Five years ago he prescribed it and expected a patient to buy and use it. Nowadays a patient knows what sodium perborate is and he will substitute some flavored and colored perborate put up under a trade name, because he knows what the official perborate is, and that it tastes bad. Manufacturers, quick to see this, retail the drug under various names and flavors. Pharmacists might suggest to the dentist that he add color and an essential oil to flavor the preparation. The psychological action of the prescription would then be retained and, after all, this is one of the most important actions of a drug.

This may sound very simple to pharmacists but that is your profession. You know how to handle coloring materials, flavors and vehicles and know how to prepare drugs in some more palatable and pleasing form. You are experienced in the *use* of these things but the average dentist, at best, has probably only read of them.

In most dental schools a practical working knowledge of these drugs is not given; the students read of them in books. They may see the drugs, but they do not have the opportunity to prepare and combine drugs as in the preparation of a prescription. Because of this, the dentist lacks confidence in writing prescriptions and encouragement or suggestions from the pharmacist to the dentist would be of mutual benefit.

Another phase in the relationship between pharmacists and dentists would be in the field of laboratory diagnosis, there is an increasing demand for pharmacists who are trained and equipped to do this work. As dentistry is becoming more of a "preventive" science there is greater necessity for dentists to have a better knowledge of the patient's general physical condition, hence, the need for laboratory tests will become greater in the coming years. In advocating this, I do not mean in any way to infringe upon the practice of medicine, but I do feel that there is much that

can be done, which will not necessitate the physician's viewpoint. To cite an example of this: In the case of gingival necrosis, commonly known as pyorrhea, with a knowledge of the blood-sugar it would be possible for a dentist, before undertaking any treatment, to know whether he would obtain a favorable result. By having a white count and a granulocyte count it would be a very simple matter to differentiate between a Vincent's infection and granulocytosis; without the blood count it means a great loss of time, which could be prevented and much error in diagnosis eliminated.

This brings up another means by which the professions may coöperate. As dentistry is conscious of its weakness in this phase of its work it has taken steps to correct it by the establishment of the Council on Dental Therapeutics. Because of the work of this Council and the interest aroused the dental colleges are giving and will, in the future, give this subject more prominence in their curricula. In the meantime there are many graduate dentists who would like to know more about the subject and postgraduate classes should be encouraged. These classes would, in my opinion, be of great value and could be sponsored by pharmacy and dental schools. I refer at this time to a course for dentists that was promoted by Prof. George C. Schicks of the New Jersey College of Pharmacy of Rutgers University. This was probably the first time such an effort has been made. This course consisted of six lectures and was attended by about thirty-five dentists. The course was devoted to dental drugs and a part of the course to the enlightenment of dentists as to what is being used in proprietary drugs. Needless to say the course was enthusiastically received. I do not mean to imply that schools of pharmacy should gratuitously establish such courses for dentists. However, there are men in the profession of pharmacy who are better fitted to teach the subject—it is their vocation and because of their general knowledge of pharmacology they may be able to suggest more efficient and effective drugs than those being used. If such men could be made available to dental societies and study groups much good could be accomplished.

Finally, I would earnestly urge that the study of your vocation never cease and that you continuously strive for improvement. A few days ago my attention was directed to a survey in the state of Michigan as a foundation to formulate a plan for socialized medicine, *i. e.*, all the divisions of public health service. In this survey it was determined that that time out of school had its influence on the individual's knowledge. This was discovered as a result of examinations consisting of questions that the average practitioner should be able to answer; it was found that the longer the average man had been out of school, the less he knew. While much is being done in the way of postgraduate work, journalism, study groups and conventions, the unfortunate part is that the man who needs this help most is the one who does not take advantage of the opportunities offered.

The author of the paper interspersed the discussion by references to the value of individual and group contact, establishment of laboratories and improvement of general knowledge.

The 30th annual meeting of the American Association of Museums will be held in Washington, D. C., headquarters at the Smithsonian Institution, May 23–25, 1935.

The AMERICAN PHARMACEUTICAL ASSOCIATION is listed among the Museums in Washington.

THE SUCCESSFUL APPLICATION OF U. S. P. AND N. F. PUBLICITY IN A RETAIL PHARMACY.*

BY LAWRENCE S. WILLIAMS.[1]

In opening his presentation the author expressed his regret that he did not promote professional pharmacy earlier. He spoke of a number of clippings from various publications, among them one by Samuel C. Davis, read before Tennessee Pharmaceutical Association, on the value and importance of manufacturing U. S. P. and N. F. preparations by retail pharmacists in the saving of costs and establishing professional relations with the doctors. Another paper, by C. O. Bigelow, was referred to; the latter had presented fifty copies of the Pharmacopœia to physicians and of these forty-nine thanked the donor, one inquired relative to the purpose of the Pharmacopœia. Another paper was by H. A. B. Dunning on the glycerophosphate preparations; all of these were referred to by the author as they awakened in him the desire to practice pharmacy more extensively and establish a prescription practice. It was this effort which enabled him to carry on.

Mr. Williams referred to the publicity of Maryland pharmacists among physicians and stated that this was producing results. He presented for consideration and thought that pharmacists should attend hospital conferences, get acquainted with the interns and medical staff; attend meetings of medical societies, pharmaceutical meetings; displays should be made at meetings and coöperative efforts should be promoted.

The author discussed the publicity developed by him; letters addressed to physicians were addressed by pen, not by rubber stamp. Among the preparations with which physicians were detailed included, "Infusion of Digitalis," "Basham's Mixture," "Stokes' Expectorant," etc. Prior to the opening of the schools, he prepared a special letter on "Vaccine Virus" and while many obtained this from the Health Department, he sold well over two hundred packages each year.

The substance of a letter addressed to doctors by Mr. Williams on "Service" is included:

"DEAR DOCTOR:

"In solicitation of your patronage, I submit a service, planned to meet the requirements of modern pharmacy in its relations with the medical profession;

"A service which does not usurp the prerogatives of the physician;

"A service which combines adequate equipment and efficient management, designed to carry out your directions;

"A service which furnishes the highest quality of prescription chemicals;

"A service which regards your patient as a sacred trust;

"A service which insures prompt delivery of your orders;

"A service at reasonable prices, which, upon your recommendation, will be adjusted to meet special circumstances of your patient;

"A service which invites your inspection."

A card, with address and phone number, addressed to prospective patrons of the section of Baltimore in which the pharmacy is located follows:

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* Section on Practical Pharmacy and Dispensing, A. PH. A., Washington meeting, 1935. Abstracted.

[1] Deceased.

"THE PHARMACIST'S CREED."

"I have given years of my life to study and training.
"I fill your needs day and night, at times without profit—at times without pay.
"I offer many courtesies and helps not known of except in pharmacies.
"I am accurate, conscientious and capable in compounding your prescriptions.
"I aid your physician in every way possible.
"I endeavor to earn the trust that you and your physician place in me.
"I am,

(Signed) Your Pharmacist,
L. S. WILLIAMS."

The author explained other means of publicity adopted and used by him and, in closing, stressed the importance of coöperation.

Some of the show globes, jars, balances and mortars donated by our late fellow-member are shown on page 947 in the September JOURNAL, A. PH. A., 1934. The Williams Pharmacy is shown elsewhere in this issue of the JOURNAL.

Mortars and Pestles, and Drug Jars Purchased by J. Leon Lascoff from the Wanamaker Collection.

Mortars and Pestles.—1, bronze, 18th century, north of England; 2–4, bronze, French, 18th–19th century; 5, Spanish, 16th century; 6, bronze, 4 rigid projections, 17th–18th century; 7, bronze, bossed with female mascarons, 17th–18th century; 8, plain bronze, 17th–18th century; 9, bronze, Spanish, 16th century.

Jars.—1, 2, Paris, decorated porcelain, about 1800; 3, 4, Italian Majolica, spouted, 17th–18th century; 5, 6, 7, 8, Urbino, 18th century; 9, Pesaro Pharmacy bottle, globular, Tankard, George I, silver, with inscription, Petley Ley, London, 1719.—Descriptions given above are incomplete, but sufficient with the illustrations to show the importance of this valuable purchase now in the Pharmacy of our fellow-member.

A PHARMACEUTICAL STUDY OF p_H.*

BY FREDERICK P. JOHNSON.[1]

FORMULATION OF p_H.

Applying the law of mass action to an acid, HA, which ionizes according to the equation $HA \rightleftarrows [H^+] + [A^-]$, we find that an equilibrium exists according to the equation

$$\frac{[H^+][A^-]}{[HA]} = Ka,$$

in which Ka = the dissociation constant of the acid. The dissociation constant of a base is given by the corresponding equation.

Water dissociates to an extremely small extent according to the equation: $H_2O \rightleftarrows [H^+] + [OH^-]$. Applying the law of mass action to this dissociation, we obtain

$$\frac{[H^+][OH^-]}{[H_2O]} = Kw.$$

The concentrations of H^+ and OH^- in pure water or in dilute aqueous solutions are so small compared with the concentration of undissociated water molecules, that the concentration of the latter, $[H_2O]$, may be considered as constant during the dissociation. The equation then becomes $[H^+] \times [OH^-] = Kw$. The value of Kw at 25° C. has been found to be 1.0×10^{-14} (5), (6), (7), (8), (21), (31). In pure water, the concentrations of the H-ions and the OH-ions must remain equal. Therefore,

$$[H^+] \times [OH^-] = [H^+]^2 = [OH^-]^2 = 1 \times 10^{-14}.$$

Then, $[H^+] = [OH^-] = \sqrt{1 \times 10^{-14}} = 1 \times 10^{-7}$. This equation means that pure water or a neutral aqueous solution at 25° C. contains 1×10^{-7} moles of H-ions and 1×10^{-7} moles of OH^- ions per liter and is a 1/10,000,000 normal solution of both H- and OH-ions.

For practical reasons, hydrogen-ion concentrations are expressed as the logarithms of their reciprocals. A common logarithm is an exponent to the base 10. Thus the symbol p_H signifies "hydrogen exponent." The definition of p_H may be given mathematically:

$$p_H = -\log [H^+] = \log \frac{1}{[H^+]}.$$

Since the hydrogen-ion concentration varies in a definite reciprocal manner with hydroxyl-ion concentration, the p_H scale may be used to express degrees of alkalinity as well as degrees of acidity, as in the following synopsis.

From this data it is seen that, while the p_H values vary according to arithmetic progression, the corresponding hydrogen-ion concentrations vary according to geometric progression.

Acidity.	Concentration of H- or OH-Ions.	Alkalinity.
p_H 7 (neutral)	N/10,000,000	p_H 7 (neutral)
p_H 6	N/1,000,000	p_H 8
p_H 5	N/100,000	p_H 9
p_H 4	N/10,000	p_H 10
p_H 3	N/1,000	p_H 11
p_H 2	N/100	p_H 12
p_H 1	N/10	p_H 13
p_H 0	N/1	p_H 14

* From the University of Washington College of Pharmacy. A thesis submitted as part requirement for the degree of Master of Science in Pharmacy under the direction of H. A. Langenhan.

[1] Fairchild fellow for 1934-1935.

FORMULATION OF BUFFER CAPACITY.

It would be of little value to discuss in this paper the action of buffers; however, since there are many references in the pharmaceutical literature to a very valuable formulation of buffer effect, this one expression will be explained here. Van Slyke (53) has adopted a unit for the buffer capacity of solutions. This unit is the differential ratio $\frac{dB}{d(p_H)}$ expressing the relationship between the increment (in gram equivalents per liter) of a strong base B added to a buffered solution and the resultant increment in p_H. An increment of strong acid is equivalent to a negative increment of base, or $-dB$. In these terms, a solution has a buffer capacity of 1 when a liter will take up 1-Gm. equivalent of strong acid or alkali per unit change in p_H. If a base is added, the p_H is increased, so that both dB and $d(p_H)$ are positive. If acid is added, both dB and $d(p_H)$ are negative. The ratio $\frac{dB}{d(p_H)}$ is, therefore, always a positive numerical value. This is called Van Slyke's ratio and is often designated by B. When this ratio is applied, for instance, to tinctures and fluidextracts, and when the buffer capacity is plotted with the quantities of acid as ordinates and the corresponding increments in p_H as abscissæ, the curve is usually a straight line within reasonable limits. From such a graph we obtain the ratio $\frac{\Delta B}{\Delta(p_H)}$ where each of these values is a measurable increment. Within the limits of the straight line curve, the buffer capacity obtained using the measurable increments is identical with that of the differential ratio $\frac{dB}{d(p_H)}$. Van Slyke's ratio is much used in adjusting pharmaceutical preparations to specified p_H values.

FORMULATION OF ELECTRODE POTENTIALS.

The most direct formulation of an electrode potential is as follows: If a metal is put in pure water, some of the metal dissolves forming positively charged ions, and consequently, the remaining metal assumes a negative charge. Three principal forces are present—the solution pressure of the metal, the electrostatic force of the charged ions, and the osmotic pressure of the solution. An equilibrium of the forces is soon reached. Assume an electrode, such that 1-Gm. mole of ions of charge n, carrying nF faradays of electricity (a faraday is the number of coulombs carried by a gram equivalent of an ion) pass from the electrode to the solution, increasing the partial osmotic pressure by dp. Thus n is equivalent to the valence of the metallic ions. The change in potential difference between the electrode and the solution will be dE. The electrical work expended will be nFdE and the work taken up by the system will be Vdp. Therefore, $nFdE = Vdp$.

According to the laws of an ideal gas, $V = \frac{RT}{p}$ in which p = pressure in atmospheres, V = volume in liters, R = the gas constant, and T = the absolute temperature. Thus, by eliminating V, $dE = \frac{RT}{nF}\frac{dp}{p}$. Integrating gives $E = \frac{RT}{nF}\log_e p + c$, where $\log_e$ is the natural logarithm to the base e, and c is some integration constant. In dilute solutions, p is equivalent to the activity of the ions. By introducing known values for R and F (R = 8.315 international joules and F = 96,500 coulombs) and, by transposing the natural logarithm into the common logarithm by multiplying by 2.3026, $E = 0.0001984\frac{T}{n}\log_{10} c\ \text{ion} + C$. Thus, at 25° C. $E = \frac{0.0591}{n}\log_{10} c\ \text{ion} + C$. C may be eliminated by equating E against ϵ_0 (normal potential of the metal, that is, the difference in potential between it and the normal hydrogen electrode in a solution whose ion activity is equal to 1). The normal hydrogen electrode is defined by international agreement according to the following specifications:

> "The potential at a hydrogen electrode under one atmosphere pressure of hydrogen in a solution of unit hydrogen activity shall be considered zero at all temperatures."

By eliminating the integration constant C, we arrive at the fundamental equation for converting electrode potentials to hydrogen-ion concentrations: $E = \epsilon_0 + \frac{0.0591}{n} \log_{10} c$ ion (25° C.).

HISTORY OF METHODS.

The electrolytic dissociation theory of Arrhenius (2) and the application of the law of mass action to ionic equilibria marked the beginning of hydrogen-ion control. The dissociation constant of water was determined in various ways by Ostwald (5), Wijs (6), Nernst (7), Kohlrausch and Heydweiller (8), Sorensen (21) and Lewis, Brighton and Sebastian (31). These steps furnished the basis for the mathematical conception of hydrogen-ion concentration. Sorensen (21) suggested that the numerical values of the negative exponents of hydrogen-ion concentration values be adopted as the basis of an acidity scale and recommended the symbol $P_H{}^+$. Clark (110) introduced the simpler symbol, p_H, which is now used more extensively.

Pertaining to the potentiometric method of determining p_H, Nernst (3), Peters (10) and Crotogino (12), using the ideal gas laws (59) and Faraday's laws of electrolysis, have shown the logical derivation of a common expression for all electrode potentials. The hydrogen electrode was first used by Bugarszky and Liebermann (9) who applied it to a biochemical problem. Later, a thorough treatise on the hydrogen electrode was published by Hildebrand (25). The calomel electrode was developed through the early efforts of G. N. Lewis and his colleagues (20), (31), (59). Our fundamental information regarding the quinhydrone electrode is largely due to Biilmann (39), (40), (56). The development of the glass electrode dates back to Helmholtz (1), who, in 1881, first constructed a glass electrode. The further development of this electrode was carried on by Haber and Klemensiewicz (19) and Kerridge (76).

The first survey of indicators suitable for hydrogen-ion determinations was performed in Nernst's laboratory in 1904 by Salessky (15). The results of this and many other surveys were summarized in Salm's famous table (16). Then came the classic work of Sorensen (21) in which he eliminated a vast number of faulty indicators and organized a series of indicators suitable for biological work. Clark and Lubs (29) also selected a series of indicators which was composed mostly of sulphonphthaleins.

HYDROGEN-ION CATALYSIS.

Most drugs can be classified into two groups on the basis of optimum p_H stability: those having maximum stability at p_H 7 and those having maximum stability very near p_H 5. This suggests two distinct factors affecting the relation between hydrogen-ion concentration and stability of drugs. Stability in the absence of acidity or alkalinity is easily understood but stability at p_H 5 must be explained on the basis of hydrogen-ion catalysis.

The majority of reactions in solution appear to be catalyzed by hydrogen ions and hydroxyl ions. The experiments of Arrhenius (4) on the inversion of sucrose by weak acids in the presence of the corresponding salt gave results which showed that the catalytic activity of acids in aqueous solution is approximately proportional to the degree of dissociation as determined by electrolytic measurements. Later Arrhenius (11) found that the rate of inversion of sucrose by weak acids was greatly augmented by the addition of the neutral salts of strong acids; for example, KCl increased the catalytic activity of CH_3COOH. Arrhenius, therefore, postulated that dissolved salts increase the dissociation constants of weak acids in solution. (Taketomi and Horikoshi (295) have recently shown that while KCl and NaCl increase the rate of sucrose inversion by acids, K_2SO_4 and Na_2SO_4 decrease the rate of inversion.) In 1900, Euler (13) proposed a theory describing the catalytic effect of hydrogen ions and hydroxyl ions as an instantaneous salt formation. This conformed to the view commonly held (but certainly not justified) that ionic reactions are more rapid than reactions between electrically neutral molecules. In 1913, Stieglitz (26) proposed a theory agreeing with that of Euler.

The view that the catalytic effect represents the result of two simultaneous changes involving a hydration of the hydrogen ion and a change in the non-ionized acid was developed by a number of workers (17), (18), (22), (24), (27). This became known as the dual theory of acid catalysis and served as the first conception of the addition products formed between hydrogen ions and other substances. Kendall (43) developed this theory and postulated that the number of catalytically active particles is much greater than is ordinarily supposed. He recognized several

types of hydrogen ions, such as H^+, $[H.H_2O]^+$, $[H.CH_3COOCH_3]^+$, $[HCl.H_2O]$, $[H.CH_2COOH]^+$, etc., existing in a complex series of equilibria and each possessing a different catalytic activity. Rice (61), in 1923, recognized such equilibria and ascribed the catalytic effect of hydrogen ions to the free ions and correspondingly to the free or unhydrated hydroxyl ions. This leads to the conclusion that stoichiometrically neutral water is distinctly alkaline catalytically, and it is not until the hydrogen-ion concentration has a value of about p_H 5 that the concentrations of the unhydrated ions become equal and the catalytic activity is at a minimum.

The views which are most in favor to-day were put forward by Bronsted (109), in 1928. Bronsted first contended that the law of mass action cannot be applied in its classical form to ionic reactions. He developed a new mathematical conception of hydrogen-ion catalysis and a new definition of acids and bases. The new definition is represented by:

$$\underset{\text{(acid)}}{A} \rightleftharpoons \underset{\text{(base)}}{B} + H^+.$$

The mechanism of hydrogen-ion catalysis can then be visualized as being a transfer of a proton from catalyst to substrate (acid catalysis) or from substrate to catalyst (basic catalysis). The success of Bronsted's hypothesis consists in its ability to predict the changes in reaction velocity due to the addition of other molecules and ions by calculating the change in concentration of the complex between the reacting substances. Bronsted's work has been verified by later investigators.

The existence of various hydrogen-ion complexes is associated with the so-called "activities" of hydrogen ions. The term, hydrogen-ion activity, will be retained in this thesis.

Olivier and his co-workers (321), (322), (323) have recently published data concerning the relation of the nature of the substrate to its sensitiveness to hydrogen-ion and hydroxyl-ion catalysis.

EFFECT OF ELECTROLYTES ON p_H.

Electrolytes have considerable influence upon both the p_H and the stability of solutions. The fundamental effect of electrolytes is by no means understood. Some of the most valuable data concerning the effects of electrolytes will be cited.

Thomas and Baldwin (34) claimed that electrolytes increase the acidity of acid solutions in the following order: $MgCl_2 > LiCl > NaCl > KCl = NH_4Cl > BaCl_2 > MgSO_4 > Na_2SO_4 > (NH_4)_2SO_4$. The sulphates decrease the acidity. Lepper and Martin (87) stated that the influence upon p_H of the cations of univalent alkali metals varies inversely as their atomic weights. They found that NaCl reduces p_H and reduces the activity of anions which results in an increased dissociation of any acids which are present. To account for their results they assumed that NaCl increases the dielectric constant of water. Loeb (33) advanced a theory which assumes that neutral salts with univalent or bivalent cations assume a charge which is negative with reference to that of water particles and that neutral or acid salts with trivalent or tetravalent cations assume a charge which is positive with reference to that of water particles. Taft and Malm (228) found that in alkaline gum arabic solutions, the presence of neutral salts increases the p_H values. Northrop (45) found that neutral salts decrease the p_H of acid gelatin and increase the rate of its hydrolysis. Britton and Dodd (257) found that NaCl in a concentration as high as tenth normal does not affect the p_H of alkaline sodium hypochlorite solution. Taketomi and Horikoshi (295) stated that the rate of inversion of sugar by acids is increased by NaCl and KCl, but is decreased by Na_2SO_4 and K_2SO_4. Schmidt (176) claimed, with regard to the flocculation of diphtheria toxin and antitoxin, that there is a range of electrolyte concentration in which no flocculation occurs. Above or below this range flocculation does occur.

PHYSIOLOGICAL p_H.

Reaction of Distilled Water.—It is well known that distilled water of p_H 7.0 is seldom obtained. Water is considerably acid after one distillation and soon becomes alkaline during storage in ordinary glass. Acree and Fawcett (142) found that the solids and carbon dioxide in once-distilled waters gave them p_H values of about 5.0–5.5. Only by repeated distillations in tin apparatus and in filtered and carbon dioxide-free air can water be obtained of p_H about 6.9. By this method the authors obtained their so-called "super-pure water" having a specific conductivity

of 0.04×10^{-6} at 18° C. Acree and Fawcett included tables which showed the errors in p_H caused by the dilution of buffers with ordinary p_H 5.0 distilled water and with p_H 5.7 air-carbon dioxide equilibrium water. Williams and Swett (55) obtained fresh, distilled water of p_H 6.8; after 48 hours in contact with air the p_H became 5.23. Stock glucose solutions had a p_H of less than 5.0. Bruck (193) has observed the change in p_H during storage of water not in contact with air. Freshly distilled samples had a p_H of 5.65; when stored in ordinary corked glass the p_H reached 9.00 in 20 days. After standing 12 days more exposed to the air, the p_H was 7.80. Freshly distilled water was sterilized in Hageda ampuls and, in 5 weeks, the p_H changed from 5.55 to 7.5–8.0. Distilled water was placed in corked flasks of Jena glass and, within 4 weeks, the p_H remained between 5.4 and 5.5. Mattheus (217) reported that water which was sterilized and stored in washed Jena ampuls for 2 years increased in p_H from 6.2 to 6.4–7.0, and increased in total solids by 0.0048 Gm. per liter. Klobusitzky (273) has devised a method for testing glass ampuls to determine if their reactions are suitable.

Adjustment to Blood p_H.—Human blood has a p_H range from 7.3 to 7.5, being fairly constant at p_H 7.4. p_H values for blood or tissues above or below these figures are not compatible with life. A patient becomes comatose if a p_H of 7.1 is reached, or convulsive with a blood p_H above 7.5. Jacobs and Parpart (210) reported that hemolysis by hypotonic solutions was measurably increased by p_H changes of as little as 0.01 unit. It is important, therefore, that the p_H of solutions for injection be as close as possible to 7.4 and that the p_H values of these solutions remain stable during sterilization.

Physiological salt solution, when prepared with ordinary distilled water, has been found by Williams and Swett (54) to be dangerously acid. Fleisch (49) has criticized Ringer's and Tyrode's solutions, claiming the first to be too acid and the other too alkaline. He reported the following method for preparing a stable, sterilizable nutritive solution of physiological p_H: To 10.5 Gm. NaCl, 0.5 Gm. KCl, 0.3 Gm. $CaCl_2$, 0.1 Gm. $MgCl_2$ and 5 cc. *N* H_3PO_4, add H_2O *q. s.* to 58.7 cc. Filter, add 50 cc. of this to 1 liter of water and sterilize. Then saturate with oxygen and add 5 cc. of sterile *N* Na_2CO_3. Hansen, Schou and Tonnesen (268) found that invert sugar solutions have a p_H of about 3.0 when the inversion occurs during sterilization in sealed ampuls. Williams and Swett (54) reported that 10% glucose solutions of p_H 8.58 became as acid as p_H 4.9 when boiled or autoclaved. In a later publication (55), they stated that when these solutions were buffered to a p_H of 7.4 with KH_2PO_4 and K_2HPO_4 there were no unpleasant reactions following their free use.

In the same article they reported the p_H values of various sterilized commercial solutions. They found that a sodium citrate solution used in a transfusion where a violent reaction followed had a p_H of 10.25. Solutions of dyes for intravenous and intramuscular injection had a p_H of 5.0. When properly buffered, 10–40% more of these dyes were excreted. Solutions of arsphenamine, tetanus antitoxin and antipneumococcus serum were all too alkaline.

The sterilization of cocaine hydrochloride is always accompanied by increased acidity. Roy (78) reported p_H values of cocaine hydrochloride solutions, as follows: 1% solution, 5.20; 2% solution, 4.50; 3% solution, 3.75. The p_H of the 1% solution, sterilized for 30 minutes at 100° C., became 4.60. Regnier and David (285), (286) observed the p_H change of cocaine hydrochloride solutions during and after sterilization. The p_H values dropped from 5.9–6.0 to as low as 3.4 after 80 days' storage following sterilization. The authors pointed out the dangers of the pharmacological use of such acid solutions. In a later publication (287) the authors found that when the cocaine hydrochloride is buffered to a weakly acid reaction by Na_2CO_3 and NaH_2PO_4 or NaH_2PO_4 and Na_2HPO_4, the p_H remains stable during sterilization.

Dietzel and Huss (111) have found that alkaline or soluble glass causes considerable p_H change during the sterilization of morphine hydrochloride solutions. The instability caused by the hydroxyl ions was found to be catalytical. They recommended the use of Jena or quartz glass. Roy (78) found that novocaine solutions become dangerously acid (p_H 4.2–4.3) during sterilization. Later, Rae (223) suggested that the only safe way of sterilizing novocaine solutions is by filtering through a Chamberland filter fitted with Jena glass. Goldberg (266) stated that the p_H of procaine hydrochloride, mixed with epinephrine, can be stabilized between p_H 5.7 and neutrality by a water solution of Na_2HPO_4 and NaH_2PO_4.

Roy (78) claimed that the hydrogen-ion concentrations of all hydrochlorides of amine alcohols increase considerably during sterilization, producing small quantities of benzoic acid.

Besides cocaine and novocaine, he considered in his article stovaine and atropine sulphate. During sterilization the p_H of stovaine dropped from 5.40 to 4.0 and that of atropine sulphate changed from 6.45 to 5.70. Macht and Shohl (37) have noted that benzyl alcohol solutions, when sterilized or stored in soft glass containers, become dangerously alkaline and deteriorate rapidly. They recommended that the solutions be highly buffered to p_H 7.0–6.8 and sealed in hard glass containers.

Levy and Cullen (36) found that strophanthin solutions, when autoclaved in commercial glass ampuls, changed in reaction from p_H 6.0 to p_H 9.0. They reported that solutions of strophanthin in 0.02 molar phosphate solution adjusted to p_H 7 and autoclaved in hard glass ampuls retained a stable p_H after 5 months.

Mulford and Greenbaum (132) have reported the change in p_H by sterilization of many pharmaceutical products, as follows: dextrose, more acid; glycerophosphate compound, more acid; iron cacodylate, less acid; magnesium sulphate, more acid; mercurochrome, more alkaline; physiological salt solution, more acid; procaine, more acid; procaine and epinephrine, more acid; sodium cacodylate, no change; sodium iodide and salicylates with colchicine, no change; sodium salicylate, more alkaline.

A general method for maintaining stable p_H during sterilization was suggested by Robertson, Woo and Sia (62). Water was twice distilled and rendered CO_2-free by passing CO_2-free air through it for 24 hours. Solutions of 7.5 molar H_3PO_4 and 7.5 molar NaOH were boiled and kept in bottles stoppered with soda-lime traps. The solute (various drugs were used) was added to the water, the H_3PO_4 was added, 1 cc. per 100 cc., and the solution brought to the desired p_H by the addition of the NaOH solution. When autoclaved, the solutions were only 0.1–0.2 p_H lower and the p_H values remained constant for 2–3 weeks. Benda (143) stated that by adding acid-binding substances, such as caustic alkalies or soluble alkaline carbonates, phosphates or acetates, to solutions of salts of *p*-dialkylaminoarylphosphinous acids, sterilizable solutions of stable p_H are obtained.

Adjustment to Ophthalmic p_H.—The adjusting of p_H is of considerable importance in ophthalmic therapy. Gifford and Denton (265) have recently conducted a detailed investigation of this problem and their results are summarized below. The reaction of the lacrimal secretions is about p_H 8.0. An acid buffer solution, suitable for ophthalmic drugs soluble only in acid media, such as zinc salts, phenacaine, cocaine and epinephrine, is made from the following formula: 6.2 Gm. boric acid, 7.4 Gm. potassium chloride and distilled water to 1000 cc. The p_H of this solution is 5.5. An alkaline buffer solution is less irritating and is a suitable medium for atropine, homatropine, physostigmine and pilocarpine. It is prepared by adding 1 cc. of a 0.20 molar sodium carbonate solution to 50 cc. of the acid buffer solution. The p_H of this solution is 7.6. The alkaline solution is, of course, a less irritating collyrium than the acid solution.

The authors stated that phenacaine is soluble in the acid solution only if the p_H is as low as 4.8. Atropine, homatropine, physostigmine and pilocarpine are soluble in both solutions but are more effective in the alkaline solution. Zinc salts precipitate in the tears unless the medium is as acid as p_H 5.5. Sodium fluorescein dissolves only at p_H 9.0 or above. Metaphen is soluble only at p_H 8.0 or above. This is the reaction of the 1:500 solution and the p_H remains unchanged when it is diluted to 1:2500. Butyn is insoluble in either buffer solution but is soluble in distilled water.

Gifford and Smith determined the following p_H values for ophthalmic preparations:

	p_H.		p_H.
1.0% atropine sulphate	5.8	4.0% procaine hydrochloride	4.6
2.0% homatropine hydrobromide	5.5	1:1000 epinephrine	4.6
2.0% cocaine hydrochloride	4.6	2.0% butyn sulphate	5.4
1.0% pilocarpine nitrate	4.8	0.9% sodium chloride	7.0
0.2% physostigmine sulphate	6.6	0.2% zinc chloride	5.0
1:1000 nupercain	4.4	Saturated boric acid	4.2

When these are dissolved in saturated boric acid their reactions vary from p_H 4.2 to 5.0.

p_H AND TOXICITY.

Alkaloids.—In 1921, Crane (41) pointed out that the toxicity of alkaloidal salts is dependent upon the degree of hydrolysis. He stated that it is not the salt or ion which is toxic and that

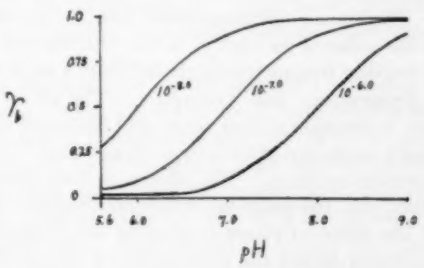
variations in the hydrogen-ion concentration affect the toxicity of alkaloids by changing the proportion of free undissociated base in the solution, rather than by direct action upon the cell. He found that with most alkaloidal salts there was 100 times as much undissociated base at p_H 8.0 as at p_H 6.0. Mayeda (116) later derived a mathematical expression for the degree of dissociation of alkaloidal salts as a function of p_H. Designating with γ_b the degree of hydrolysis of a salt composed of a strong acid and a weak base (alkaloidal salt) with a dissociation constant K_b, and with Kw equal to the dissociation constant of water, it was shown that

$$\gamma_b = \frac{Kw}{Kw + K_b\,[H^+]} \text{ or } \gamma_b = \frac{Kw}{Kw + K_b.\,10^{-pH}}.$$

This equation shows that γ_b is independent of the concentration of the alkaloidal salt but is dependent upon the magnitude of the dissociation constant K_b the base or free alkaloid playing the rôle of a parameter. Mayeda plotted these functions (cf. Fig. 1) with the degrees of hydrolysis as ordinates and the p_H values as abscissas. Referring to the graph, it is noted that each curve has a turning point at which the degree of hydrolysis has the value 0.5. If $pK_b = 7.0$, the hydrolysis varies as follows:

p_H	5.5	6.0	7.0	8.0	8.5
% of hydrolysis	3.2	9.1	50.0	90.9	96.9

Assuming that the free alkaloid alone is biologically active, the activity is almost twice as great at p_H 8.0 than at p_H 7.0. Using cinchona alkaloids, Mayeda experimentally verified his mathematical results. He concluded the following: 1. The biological action of cinchona alkaloids is dependent entirely upon the amount of alkaloidal base freed by hydrolytic dissociation which, in turn, is a function of the p_H. 2. Only the free quinine base is the bearer of biological action.



Hydrolysis Curves of Alkaloidal Salts with Dissociation Constant $K_b = 10^{-6}, 10^{-7}, 10^{-8}$

Fig. 1.

Gerlough (204) obtained the following results pertaining to the effect of p_H on the actions of local anesthetics as measured by the rabbit cornea method. The duration of anesthesia produced by procaine hydrochloride, procaine borate and butyn increased with increasing p_H. Duration of anesthesia by butesin picrate was unaffected by changes in p_H. Butyn and procaine hydrochloride in buffered solutions had greater action than in unbuffered solutions of the same p_H. Fosdick, Hansen and Dragstedt (151) also reported that an increase in alkalinity augmented the anesthetic properties of procaine and cocaine hydrochloride solutions. Their investigations showed that the efficiency of procaine borate and hydrochloride is practically the same at p_H 8.4, but that the borate is more efficient at higher p_H values and the hydrochloride is more efficient at p_H values below 8.4. In general, these results with local anesthetic also point to increased biological activity when a greater amount of alkaloidal base is freed by dissociation.

Cosmetics.—Eggerth (80) has published the results of a detailed investigation concerning the effect of p_H on the germicidal action of soaps. Eggerth found for all soaps an acid and an alkaline range in which the soaps were most germicidal. Potassium butyrate was non-germicidal in a concentration of tenth-normal at all p_H values within the limits of 3.8 to 10.5. He stated that solutions of soaps having 12 or more carbon atoms in the molecule were alkaline in reaction, and that increasing the number of carbon atoms in the chain increased the alkalinity of the solution due to increased hydrolysis. With increasing molecular weight of the soap, the germicidal titer increased to a maximum and then diminished, the point of inflection varying with the p_H and the organisms. Thus, with B. typhosus at p_H 5.5 the titer rose with increasing molecular weights up to capric acid and then diminished. With most organisms, the maximum titer for the acid range was reached with lauric and tridecylic acids. In the alkaline range the germicidal action increased

with molecular weight to the palmitate and then diminished. The lower members of the saturated series of soaps were found to be most germicidal in an acid reaction. For instance, the titer for potassium caprate was 1000 times as great at p_H 4.4 to 4.7 as it was at p_H 9.0 to 10.0.

Eggerth proposed the following explanations concerning the relation between p_H and the germicidal action of soaps. 1. Hydrogen ions and hydroxyl ions may affect the bacterium rather than the soap. 2. An acid reaction may decrease the surface tension of the soap and thus increase its concentration at the surface of the bacterium. 3. The p_H effect may be due to alterations of the solubility of soap in the aqueous phase or in the bacterial protoplasm. 4. The fatty acid may have a greater germicidal action because the acid is less dissociated than the soap, and there is evidence that undissociated molecules penetrate more readily into protoplasm than do ions.

Janistyn (211) called attention to the value of certain acids (anisic, formic, benzoic, butyric, citric, acetic, gallic, tannic, glycerophosphoric, camphoric, etc.) in concentrations giving a therapeutic skin p_H of 3.0 to 5.0 in soaps, skin, mouth and hair preparations and other cosmetics. Janistyn stated that the disinfecting action of buffered acids is greater than that of unbuffered acids because of the higher acid-ion concentration. An anonymous article in the *Drug and Cosmetic Industry* (302) stated that the normal p_H of skin is between 4.5–5.0 and that any cosmetic which has a strong alkaline reaction is detrimental to the skin. This article stated that the p_H range of blood is from 7.0 to 7.4 and that face creams whose p_H values deviate from this range cause irritation to the epidermis. The author also pointed out the existence of acid and alkaline ranges wherein an optimum effect can be obtained from antiseptic lotions. Mayer (320) has shown the value of p_H control in the manufacture of shampoos and has stated that a properly designed soapless shampoo base should have a p_H of about 7.0 to 7.5.

Preservatives and Antiseptics.—The preservative action of acids and bases is, in a large measure, a function of hydrogen- and hydroxyl-ion activity, and also, specific effects which were previously suspected of certain acids and bases have now been clearly demonstrated by the use of hydrogen-ion methods. The effects of these ions are greatly complicated by various conditions associated with the colloidal phases and degrees of permeability of cell membranes. The alternation of the colloidal phase conditions often depends upon the inorganic ions which are present. Thus, calcium favors the permeation of oil-soluble substances and sodium of water-soluble substances. An interesting feature of permeability is that weak acids or bases penetrate cells readily, whereas strong ones fail to do so. The direct action of hydrogen-ion concentration upon cells must be kept distinguished from its control of the effective state of a toxic compound. The relationship between p_H and toxicity to microörganisms is discussed below in three phases: The preservation of foods, the preservation of drugs and the effect of antiseptics in therapy.

In 1929, Cruess and Richert (124) found that the concentrations of sodium benzoate required to prevent the growth of yeasts, molds and bacteria were greatly affected by the p_H values of the medium. In a later publication (195), Cruess, Richert and Irish stated that the concentration of sodium benzoate necessary to give the same preservative action at the neutral point as at p_H 3.0 was 200 times as great. Still later, Cruess (236) observed that for the destruction of fermentation organisms, 4% of sodium benzoate was required at p_H 7.0, 0.06–0.1% was required at p_H 3.5–4.0, and 0.02–0.03% was required at p_H 2.3–2.4. He stated that some molds grew profusely in a 10% sodium benzoate solution of p_H near neutrality. In asparagus juice, Clostridium botulinum grew and formed toxin at p_H 7.4 with 0.8 Gm. of sodium benzoate per 100 cc. The organism did not grow at p_H 4.7 with 0.1 Gm. of the preservative per 100 cc. In regard to other salts of weak acids, it was stated that in the p_H range 5.0 to 9.0 the necessary concentrations of sodium salicylate, sodium sulphite and potassium acetate were considerably higher than in the p_H range 2.0 to 4.5. From these observations Cruess concluded that the undissociated weak acids, rather than their ions, are the preservative agents. This conclusion is in direct accordance with that of Eggerth (80) who stated that undissociated molecules penetrate more readily into protoplasm than do ions. Cruess' observation that lowering the p_H did only slightly enhance the preservative actions of sodium chloride and formaldehyde also supports the conclusion of Eggerth.

In 1932, Back (233) reviewed the use of preservatives in pharmaceutical preparations. He stated that concentrations of vinegar, equivalent to 2.5–3.5% of acetic acid, are sufficient to prevent fermentation in sauces and similar preparations. Lactic acid is satisfactory as a preservative but there is evidence that citric acid in equivalent strength is less effective. He stated that in

addition to the p_H value, the nature of the anion affects the preservative properties. If sugar is used, the concentration must be 66% or above. He also stated that, in general, a concentration of 8–15% of salt inhibits bacterial growth but that many yeasts grow in a 25% salt solution; even concentrated brine will not kill spores. Walbum (297) found that the resistance of earth spores to destruction was greatest at p_H 8–9 and quickly decreased on the acid and alkaline sides.

The effect of insulin solutions (20, 32 and 40 units per cc.), without preservatives, and of a solution of 40 units per cc. with 0.3% tricresol on the viability of Staphylococcus albus, was studied by Hartley (208). Solutions of p_H 3–4 had a germicidal action with no preservatives present. When the normal acidity of a solution containing no preservative was even slightly reduced, staphylococci were not killed and considerable growth occurred at p_H 6.0. When p_H 8.5 was reached, the solutions, in most cases, again did not allow growth of staphylococci. It seems that the insulin itself has a toxic effect on microörganisms because, on ordinary culture media, staphylococci develop most favorably in a slightly alkaline reaction and growth is not inhibited by p_H changes from 5–9.

With regard to the British Liquor Arsenicalis, Milne and Rattray (280) found that when organic matter was completely excluded during preparation, very little growth of molds occurred at temperatures suitable for their rapid development and that the growth was most at p_H 7.0.

Joachimoglu (57) has investigated the influence of p_H upon the antiseptic effect of mercuric chloride solutions buffered with glycocoll, NaOH and HCl. The final dilutions of mercuric chloride were 1:672,000. There was strong antisepsis at p_H 3.3–4.0, no effect at p_H 7.8–10.1, a slight effect at p_H 10.5, and strong antisepsis at p_H 11–12, corresponding to that between p_H 3.3–4.0. When buffered with secondary sodium citrate and sodium hydroxide, positive antiseptic action was obtained between p_H 5.0–6.6.

Daniels and Lyons (196) have studied the effect of p_H upon the antiseptic actions of phenyl substituted acids from benzoic to ϵ-phenyl caproic. They could find no definite relation between p_H and antiseptic effect but did note that there was a gradual rise in p_H as the series ascended. They found the antiseptic actions of certain phenols to be strongest in an acid range below p_H 4.5 and in an alkaline range above p_H 10. They also stated that the undissociated acid molecule is the active portion in disinfection by means of acids, whereby the antiseptic action would be inversely proportional to the hydrogen-ion concentration. Janistyn (211) claimed that the disinfecting action of acids is greater when they are buffered because of the higher acid-ion concentration. He cited experimental evidence to show that lactic acid and sodium lactate of p_H 3.7 in a concentration of 1:15 is equivalent in disinfecting power to 65% ethyl alcohol.

Kunzmann (275) has stated that hydrogen-ion concentrations between p_H 6.5–7.5 had no effect upon the disinfecting properties of potassium iodide and sodium iodide solutions. He found that potassium iodide was more effective than sodium iodide but that the effect of both was decreased when they were mixed.

p_H AND STABILITY OF DISPERSED PHASES.

Before entering into the discussion of the relation between p_H and the stability of drugs, it will be of value to consider the work performed by the Swiss pharmacists, Tschirch and Fluck (119), (125), on instability caused by the presence of acacia. They have found that acacia contained one or more oxidizing enzymes and that these enzymes attacked most alkaloids and glucosides. The manner of action on morphine indicated that the oxidases attacked especially the free hydroxyl groups. Acacia, which had been inactivated, did not oxidize morphine. It was found that the oxidases of gum arabic were able to act in a pill mass with a moisture content of 2% or above. Tschirch and Fluck found that the acacia could be inactivated, as shown by the guaiac and benzidine test for oxidase, by boiling a mucilage to dryness, or by precipitating the gum with boiling neutral alcohol. The authors pointed out that precipitation of the gum by acid alcohol produced an inactive powder which, after completely washing out the acid, would not dissolve in distilled water but which required an alkaline condition for solution.

Emulsions.—The preparation of stable emulsions has been for many years a disconcerting problem. When emulsions were conceived as a fine dispersion of one liquid in another, the size of the dispersed particles was considered to be the only important factor controlling the stability. Later investigations have shown that a purely mechanical conception is not sufficient and that emulsion formation is affected by factors similar to those affecting colloid formation.

Different emulsifying agents have been found to cause opposite phase dispersions and to cause different ranges of stability along the p_H scale. Harkins (30) has stated that sodium oleate and similar compounds produce emulsions of the oil-in-wate. type, whereas calcium and magnesium oleates and other compounds in which 2 hydrocarbon radicals are attached to 1 metallic atom produce water-in-oil emulsions. Harkins found that emulsions produced by magnesium oleate disintegrated when the p_H of the aqueous phase became as low as 2.5. He attributed this disintegration to the decomposition of the emulsifying agent, which must be in contact with the dispersed phase. Krantz and Gordon (113) substantiated Harkin's results and stated that with magnesium oleate emulsions the most stable p_H range of the internal phase was between 11–12.5. The same authors (130) found that in magnesium oleate emulsions, the size of the dispersed particles varied between 17–30 microns. They also stated that with this type of emulsion, p_H did not significantly affect the surface tension, that there was a decided drop in viscosity on the acid and alkaline sides of the p_H range 0.9–13.0, that the emulsions in mineral oil were unaffected by the addition of sodium chloride, but that the emulsions in olive oil were made less stable by the addition of sodium chloride. The authors concluded their discussion of magnesium oleate emulsions by stating that the most important factor in the stability of these emulsions is the influence of the hydrogen-ion concentration of the dispersed phase upon the magnesium oleate.

Krantz and Carr (242) recommended the use of magnesium oleate in the preparation of Ointment of Rose Water because it produced a neutral, stable and compatible water-in-oil emulsion. They stated that all salts producing an hydroxyl-ion concentration represented by p_H 9.17 or above produced satisfactory ointments.

Krantz and Gordon (86), (113) found that oil-in-water emulsions produced by acacia had a wide stability range within p_H 1.6–10.35, with greatest stability between p_H 4.11–4.28. The results were the same whether the oil was vegetable or mineral, or whether the acid used was hydrochloric or sulphuric. Addition of sodium chloride showed that the chlorine ion did not influence stability. The surface tension varied slightly with p_H, being a maximum at p_H 7.3 and decreasing by about 30% at the acid and alkaline extremes. Viscosity was unaffected by p_H. The size of the particles was smallest near p_H 7 and increased considerably with increasing p_H values and increased very little with decreasing p_H.

The same authors found that oil-in-water emulsions produced by tragacanth had a range of greatest stability within the p_H limits of 1.9–2.3 and had another, more narrow, and less stable range, at about p_H 6.3. Tragacanth emulsions differed also from acacia emulsions in that their viscosity decreased with increasing p_H. In considering gels of tragacanth, the authors found that only those between p_H 0.4–2.1 remained free from the separation of water at the surface. The most stable range of p_H for tragacanth emulsions lies within this scale. The authors claimed that this supports the hydrate theory of emulsions[1] which posulates that oil is most thoroughly emulsified in a hydrophile colloid when just a sufficient amount of water is present to form a hydrate. With tragacanth, according to Krantz and Gordon, this amount of water is evidently a function of its hydrogen-ion concentration. Therefore, at the p_H value where tragacanth possesses the highest degree of hydratability, this value is the most stable point for emulsions prepared with tragacanth.

Krantz (129) has investigated the buffer actions of both acacia and tragacanth. The buffer capacity $\frac{\Delta B}{\Delta p_H}$ of acacia was found to be 0.034 and to extend over a wide range. Since acacia consists of the K, Ca and Mg salts of a weak acid, its buffer capacity is more effective in the neutralization of acids than of alkalies. This was shown by Krantz when he plotted the buffer capacity (cf. Fig. 2). At p_H 10.5 the curve became very abrupt, but below 2.5 the curve descends as a gradient. This accounts for the extreme instability beginning on the alkaline side of the p_H stability range. Tragacanth exerted considerable buffer capacity between p_H 3.0–10.0. In view of the wide buffer capacities of these two emulsifying agents, Krantz (165) attempted to increase their stability ranges by buffering the external phases. With acacia, no increase in stability was observed between p_H 2–10.5, but with tragacanth, the stable range of 1.9–2.3 was increased to p_H 1.9–5.0.

On account of the sharpness of the single break in the titration curve of acacia, Taft and Malm (228) have claimed that arabic acid is evidently a strong monobasic acid. They explained

[1] Fischer, "Fats and Fatty Degeneration," page 5 (1917).

the viscosities, densities, freezing points and conductances of acacia solutions of widely variable concentrations by assuming that acacia acts as a strong organic electrolyte rather than as a colloidal phase when in contact with water. They attributed the protective action of acacia solutions to their high viscosity and to the probable high adsorption of the acacia molecules.

According to Friedman and Evans (203), the stability of gelatin emulsions is dependent upon the p_H, and, to a small degree, the concentration of the gelatin. The stability range, in general, was between p_H 3–6, with a few emulsions becoming very unstable near p_H 3 when the gelatin concentration was as low as 0.25%. When the p_H of the gelatin solution was near the isoelectric point (about p_H 4.95), the most stable emulsions were formed. Stability sharply decreased at p_H of about 3.0, there was another point of increased stability near p_H 2.5, and a sharp drop in stability when the p_H was further decreased. Addition of alkali resulted in a marked decrease in stability above p_H 6.0, with another range of stability near p_H 8–10, and another decrease when the p_H rose above 11. A summary of these results shows that there are two p_H ranges for stability, one from p_H 3–6, and the other in the vicinity of p_H 8–10. This is in accordance with the results of Kraemer (85), who reported finding two isoelectric points for gelatin, one at p_H 4.95, and the other near p_H 8.

Enz and Jordan (239) reported the following results after investigating the ease of emulsification of alkaloid-containing preparations. Fluidextract of Belladonna Leaves showed least emulsification at the neutral point; Tincture of Stramonium and Fluidextract of Cinchona showed least in acid solution, and Fluidextract of Hydrastis and Tincture of Nux Vomica showed no uniformity. According to the authors:

> "The results indicate that the statement, 'emulsions are less apt to form in strongly acid or alkaline solutions than in those which are neutral,' is true only in specific instances."

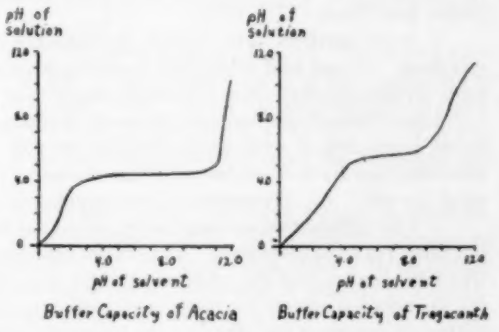


Fig. 2.

According to some experimental work reported by Weeks (185), at p_H values less than 7.0, the area of a water-spread emulsion for a given pressure increased with time without reaching an equilibrium. At p_H values above 7.0, the area finally became constant with time but the values were large and were dependent upon the p_H. At p_H 7.0, the water-spread emulsion showed a constant area with time for a given pressure and quickly reached the equilibrium.

Colloids.—Unless conditions are favorable, a colloidal solution may be a very transient system. There are many pharmaceutical colloids representing and acting as transition cases between the two practical classes of colloidal solutions. Thus, gelatin, acacia, albumen and mercury ointments represent the class of reversible or lyophile colloids, and metallic suspensions and the two silver protein preparations represent the irreversible or lyophobe colloids. A consideration of the stability of colloidal solutions reveals two important stabilizing agencies, solvation and electric double layers, the former being typical of lyophiles, the latter of lyophobes.

Considerable work has been done concerning the effect of acid-base equilibria on the stability of colloids. Those colloids of the lyophile class, representing mostly the effects of macromolecular solvation, are less affected by ionic phenomena than are those of the lyophobe class. Electric double layers are responsible for the stability of most hydrosols of inorganic substances in the absence of protective colloids and these layers are sensitive to the charges of electrolytes. According to theory, as two particles carrying electric double layers approach each other, the outer layers are deformed or polarized and an electrical repulsion results. The electrokinetic potential necessary to prevent adhesion is considered to be about 15–25 millivolts. Since the potential of non-ionic and sparingly soluble ionic particles in water is not so large, stability usually requires the presence of a definite amount of an electrolyte, one ion of which is adsorbed by the particle.

In 1922, Bogue (46) showed that various physical properties of colloids, including the viscosity, jelly strength, melting point and joining strength, were a minimum at a p_H corresponding to the isoelectric point. As the acidity or alkalinity increased from this point, these properties rose in value. In 1925, Johnston and Peard (75) determined the isoelectric point of gelatin as p_H 4.7. The surface tension was a maximum at this point and a minimum at p_H 3.8–4.0, and in the neighborhood of p_H 9.0. A second maximum was found at p_H 2.8–3.0, below which the surface tension steadily decreased. Addition of electrolytes also lowered the surface tension. A year later, Kraemer (85), using the Tyndall effect to designate the isoelectric point of gelatin, determined the point as p_H 4.9; the Tyndall effect indicating a maximum tendency to precipitate at this point. He suggested a second isoelectric point near p_H 8 where there was a distinct decrease in light dispersion. The maximum gel strength appeared on either side and very near to the optimum precipitation point, or isoelectric point, illustrating that gel formation takes place under conditions which are just adjacent to those leading to readiest precipitation or coagulation. Kraemer stated that, contrary to the usual assumption, the gel formation was very small within a narrow range at the isoelectric point.

Recent literature reflects considerable interest concerning the effects of hydrogen ions and other ions on the swelling of gelatin. This phenomenon has nothing to do with the decomposition of gelatin or with the destruction of the colloidal state, but rather it is caused by the production of a higher osmotic pressure within the separate particles of gelatin, due to a Donnan equilibrium set up between the particles. Concerning this subject the reader is referred to J. Loeb[1] and Miller and Pleass (131), (173).

Many workers have studied the influence of hydrogen ions on the coagulation of colloidal solutions. Ghosh and Dhar (82) have explained the coagulation by electrolytes of solutions of ferric hydroxide, chromium hydroxide, mastic and gamboge, according to the following principles: 1. Adsorption of ions carrying the same charge as the sol. 2. Hydrolysis of the sols and consequent generation of acids which stabilize the sols. Addition of acids renders the sols unstable by checking their hydrolysis, but addition of alkalies increases the stability by increasing the hydrolysis of the sols. 3. Hydrolysis of the coagulating electrolytes.

The explanation of coagulation which has been offered by Hazel and Sorum (209) is similar but more readily acceptable. They claim that for a positive sol (there are both positive and negative sols), the anion of the added electrolyte is the effective agent in producing coagulation. Hence the flocculation values for monovalent ions are higher than for bivalent or trivalent ions. The authors determined the effects of the following groups of electrolytes upon ferric oxide solutions:

1. Univalent salts.
2. Bivalent salts represented by $BaCl_2$.
3. Trivalent salts represented by $FeCl_3$ and $AlCl_3$.
4. K_2SO_4, $(NH_4)_2SO_4$, $CaSO_4$.
5. K_2CrO_4 and $K_2Cr_2O_7$.
6. $K_3Fe(CN)_6$ and KH_2PO_4.
7. $K_4Fe(CN)_6$.

The flocculation values decreased for Groups 1, 2 and 3, respectively. In Groups 1, 2, 5 and 6, the flocculation values decreased with increasing hydrogen-ion concentrations. The effect of electrolytes of Group 3 did not vary with p_H, both electrolytes being salts of a strong acid and weak base, whereby their hydrolyses produced a constant p_H. The flocculation values of the electrolytes in Group 4 increased with increasing hydrogen-ion concentrations. Bedford, Keller and Gabbard (256) have also reported that the presence of sulphates caused the stability of ferric oxide solutions to vary inversely with the hydrogen-ion concentration.

Morton (220) has performed electrometric studies which have revealed the complex formations and colloidal conditions of pharmaceutically important iron compounds. Electrometric titrations were performed to determine the cause of the non-precipitability by volatile alkalies of solutions of iron "citrochloride." This was found to be due to the formation of the basic colloid-complex, $FeC_6H_5O_7.2Fe(OH)_3$. In the absence of complex formation, that is, without the addition of citric acid or alkali-metal citrates, the red color of basic iron salts was exhibited at p_H 2.2, and

[1] "Proteins and the Theory of Colloidal Behavior" (1924).

at p_H 2.36 the solution became colloidal. Coagulation occurred at p_H 6.48. This indicated that only in strongly acid solutions can the ferric ion exist in an appreciable concentration.

Morton reported that Fehling's solution consists of a basic colloid-complex, $3CuC_4H_4O_6.5Cu(OH)_2$, peptized by excess of tartrate ion. He explained that the cataphoretic behavior of the hydrosol is due, not to the presence of complex anions, but to the negative colloid-complex.

In a later work, Morton (221) reported that in pharmaceutical mixtures of the ferric chloride-sodium salicylate-bicarbonate type the iron is present partly as a violet crystalloid complex, $Fe(OH)_2(C_6H_4OHCOO)$, and partly as a red basic hydrosol, the proportion of the metal present in each form depending on the degree of acidity or alkalinity. In acid solutions, the hydroxy-acid complexes of iron were found to be present mainly as true electrolytes, but in alkaline solutions they were decomposed to varying extents with the formation of basic hydrosols. Their apparent stability in alkaline solution was assumed to be due to the peptizing and protecting properties of the hydroxy-acid anion.

p_H AND STABILITY OF COMPLEX PRODUCTS OF BIOLOGICAL ORIGIN.

Proteins.—The vast amount of investigation dealing with the structure of proteins have given rise to much information concerning the effect of p_H upon the decomposition of proteins. Although most proteins do not require stabilization, the general principles concerning their decomposition are of wide scientific interest and can be applied to the problem of stabilizing toxins, antitoxins and insulin.

Northrop (45) has studied the decomposition of gelatin and has reported that in acid solutions of p_H less than 2.0, the velocity of hydrolysis was directly proportional to the hydrogen-ion concentration, and that in alkaline solutions of p_H greater than 10.0, the velocity was directly proportional to the hydroxyl-ion concentration. Between p_H 2.0 and 10.0 the rate of hydrolysis was approximately constant and was much greater than would be calculated from the hydrogen and hydroxyl-ion concentrations.

In 1930, Svedberg (181) published some generalized results related to the p_H stability regions of proteins. He found a number of proteins to be monodisperse, that is, homogeneous as to molecular weight. They were divided into two groups; the first containing those with molecular weights from 34,500 to 208,000, the second containing those with molecular weights in the millions. Those of the first group fell into four classes, with molecular weights 1, 2, 3 and 6 times 34,500. The monodisperse proteins had a wide stability region, usually between p_H 3–11, and including the isoelectric point of the protein. This point was never in the middle of the stability region but was always shifted in the direction of the low p_H values. The protein molecules containing more than one group of weight 34,500, split into molecules of $^1/_2$, $^1/_3$ and $^1/_6$ of the original as the p_H value was raised. At sufficiently high alkalinity all proteins had the molecular weight 34,500. The same results were obtained by lowering the p_H. This decomposition was reversible in many cases. When the mixture was restored to a p_H within the stability range, molecules of the original weight were built up out of the fragments.

Sjogren and Svedberg (178) found that egg albumen was stable with regard to molecular weight in the p_H range 4–9. The decomposition was measured by the velocity of sedimentation caused by ultracentrifuging. At p_H values below 3 the sedimentation increased, indicating the formation of aggregates of denatured proteins; at p_H values above 9 the sedimentation decreased, indicating the breaking up of the molecules. The molecular weight was determined as 34,200.

Svedberg and Heyroth (137) studied the p_H stability of hemocyanin, which has molecular weights of 5,000,000. The molecular weight was constant between p_H 4.5–7.4. As these limits were approached, the protein molecules became hydrated, and, as the limits were exceeded, they rapidly disintegrated into smaller particles of undetermined magnitude. The acid disintegration was reversible in its earliest stages but the disintegration of the products first formed continued slowly and was irreversible in its later stages.

Nasset and Greenberg (133) have studied the rate of hydrolysis of casein in acid solutions. They claimed that the effect of acids was catalytic in nature and reported that the hydrolysis was proportional to the hydrogen-ion activity of the acids. The velocity constant for the three acids used decreased in the following order: HCl, H_2SO_4, H_3PO_4. The rate of hydrolysis conformed to the equation for a reaction of the second order.

In 1925, Brownlee (73) generalized his observations concerning the stability of toxins and

lysins by stating that the optimum p_H for the stability of these substances varied from p_H 6–7.5. His observations showed that the decomposition at ordinary temperatures was slower on the alkaline side than on the acid side. Schmidt (176) reported that diphtheria toxin was stable at 18° C. between p_H 6.5–9.0, while at p_H 5.4 or 9.9 the antigenic power was slowly destroyed, even when the temperature was 0° C. At 37° C. and p_H 7.0 the antigenic power was destroyed. Flocculation by mixtures of toxin and antitoxin was prevented when the mixtures were freed from electrolytes or when the electrolyte content exceeded certain limits which varied greatly with different concentrations. The flocculating power of the antitoxin decreased with increasing temperature and alkalinity. The condition was reversed by acidifying. Schmidt stated that diphtheria antitoxin was much more stable to the destructive action of salts than was the toxin, and that salts of oxidizing and reducing acids and of certain aromatic acids completely destroyed both the toxin and antitoxin. Neutral salts had almost no influence.

With regard to tetanolysin, a component of tetanus toxin, Schrek (292) stated that acidification decreased the rate of heat inactivation of the lysin and that alkalization accelerated the heat inactivation. Acidification of the lysin to p_H 4.0 decreased the rate of oxidation, and acidification below p_H 4.0 increased the rate of oxidation. Acidifying to p_H 3.0 caused considerable inactivation in the absence of heat or oxidation. This indicates maximum stability of tetanus lysin near p_H 4.0.

Much work of a similar nature has been done concerning the decomposition and precipitation of serum proteins (81), (100), (156), (180).

Remesow (174) has achieved some interesting results bearing on the coagulation of l cithins and cholesterins. The solutions of both were lyophobe colloidal solutions of suspensoid character. The coagulation limit for cholesterins was p_H 4.0; for cholesterin esters, p_H 2.0; and for lecithins, between p_H 6.2–5.6. The flocculation optimum for lecithin solutions lay between p_H 2.8–2.0. A large number of substances, the most important biologically, such as egg white, hydrocarbons, alkaloids, ferments, etc., were found to sensitize the lecithins and cholesterins in such a manner that their coagulation values were displaced to different p_H values. Tables were included which showed the precipitation or lack of precipitation of cholesterins, cholesterin esters, lecithins and hydrolecithins at various p_H values and under the sensitizing actions of more than 50 physiologically important substances and drugs. This so-called sensitizing action was proved to be one not between the substance and the sensitizer as in ordinary precipitation.

Hormones.—Krogh and Hemminsen (114), in 1928, reported that the optimum p_H range for insulin stability was between p_H 2.0–4.0. This optimum range has been modified later. The authors reported a distinct alkaline shift during decomposition and stated that the solutions became opalescent above p_H 4. Gaddum (152) also found the stable range for insulin to be from p_H 2.0–4.0 and reported exceedingly rapid decomposition above p_H 7.0 and below p_H 1.0. In 1931, Sjorgren and Svedberg applied ultracentrifugal methods for measuring the decomposition of insulin and thereby determined the p_H range for optimum stability to be between p_H 4.5–7.0. Near the borders of this region the decomposition was reversible. By ultracentrifugal means, the authors determined the molecular weight (35,100), sedimentation constant, molar friction constant and molecular radius. The values were very nearly identical with those for egg albumen. Mogilskii (218) has reported that the isoelectric point of insulin was between p_H 4.3 and 5.7, depending upon the purity of the solution.

Freudenberg and Eyer (201) have investigated the destructive action of acids and alkalies on insulin. The extreme instability to alkalies was evidently due to the cleavage of 2 molecules of NH_3. One molecule of NH_3 was attacked by oxidizing agents and the other by reducing agents. Acids caused separation of NH_3 by hydrolysis. Wintersteiner (298) found that by varying the p_H between 6.0–8.0, and using cysteine, thioglycollic acid and alpha thiolactic acid as reducing agents, with all three compounds the rate of inactivation of insulin increased with increasing p_H.

The control of p_H is of special importance in the preparation of pituitary extracts free from animal protein. Whenever the protein is precipitated, a certain amount of the pituitary principles is destroyed. It is desirable to obtain a p_H value whereby the best possible compromise can be attained between the amount of protein destroyed and the amount of active principles remaining. The original work was done by Dudley (32), Abel and Nagayama (35), and Stasiak (90) who pointed out the acid lability and the extreme alkaline lability of both the oxytocic and vasopressor

constituents of pituitary. Abel and Nagayama observed that the acid destruction of the extracts caused the formation of histamine which produced a lowering of arterial pressure instead of the desired increase. Gaddum (152) stated that for the oxytocic principle the effect of variation of the p_H was a minimum between p_H 7–8, but that the absolute optimum p_H for stability was 3.0. The presence of salts caused a very small increase in destruction. Gaddum summarized his results in a table which gives the amount of destruction of the oxytocic principle to be expected, when a solution of any p_H is heated at any given temperature for any given time.

Gerlough (153) carefully measured the amounts of inert protein which were precipitated by various reagents and at various p_H values when the pituitary extracts were placed in boiling water for 12–14 minutes. These results are summarized in Fig. 3 and can be compared with the p_H stability curve for oxytocin formed from Gaddum's data for the same temperature and same duration of time. The tungstic acid curve shows the greatest precipitation of protein but this reagent must be excluded because only 30–40% of the oxytocic principle re nains after treatment. A comparison of the two graphs shows that although the maximum stability occurs at p_H 3.0–3.4, the maximum precipitation of inert protein which allows only a reasonable decomposition of the active principle can be obtained when the extract is adjusted to p_H 4.4 with acetic acid.

The hydrolysis of acetyl choline was investigated when a relation was suspected between it and the oxytocic pituitary principle. Gaddum (152) found the optimum p_H for its stability to be 3.9. Hofmann (157) found that the hydrolysis of acetyl choline chloride solutions produced an acid reaction which gradually checked the hydrolysis. The least hydrolysis occurred at p_H 3.9 with considerable hydrolysis occurring at p_H 5.0. The cleavage of acetyl choline was considerably depressed by the addition of non-electrolytes, such as antipyrine and acetamide. The effect of acid upon the racemization of *l*-epinephrine has been investigated by Haddock (267). In 10% hydrochloric acid, a solution of *l*-epinephrine was completely racemized in 12 hours, but in normal hydrochloric acid (3.6%), racemization was only 58.5% in 216 hours. In the latter case, 10% was destroyed by oxidation. In HCl solutions of p_H 1.4, the racemization of 1% epinephrine was negligible, even with exposure to ultraviolet light. Barker, Eastland and Evers (234) found that the oxidation of epinephrine by potassium persulphate was most rapid at p_H 5.6, the rate of oxidation being one-fourth as great at p_H 4.7 and 7.1. The presence of small quantities of copper greatly increased the rate of oxidation and iron showed a slight inhibitory effect.

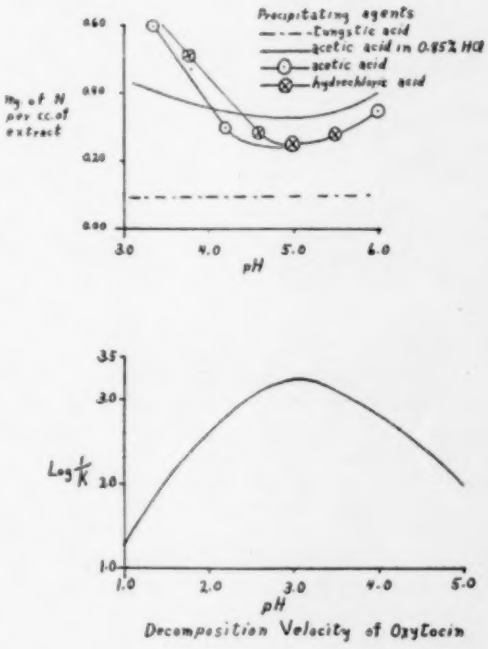


Fig. 3.

Marshall (278) stated that the *p*-factor of the gonadotropic hormones lost 50% of its activity in 17 days when adjusted to p_H 7.0 and preserved with 0.5% phenol.

Vitamins.—The experimental work concerned with the stability of vitamins can best be summarized in the following table. The experiment represented by the first tabulation for the B_2 factor, in which no decomposition occurred, was performed upon a liver concentrate.

Enzymes.—A discussion of the relation between p_H and the activity of enzymes is far beyond the scope of this paper. It is sufficient to say that each enzyme has an optimum p_H for action and that changes in enzyme activity with changes in p_H are evidently related to the state of ionization of the substrate and the enzyme. References are: (21), (23), (51), (67), (73), (101), (104), (117), (207), (232), (283).

Vitamin Factor.	Temperature.	Time in Hours.	p_H.	% Decomposition.	Reference.
B_1	100°	24	1.0	0	126
	120°	1	6.0	0	135
	100°	1	5.2	10	89
	100°	1	7.9	30–40	89
	100°	24	5.0	50	126
	100°	1	9.2	60–70	89
	100°	1	10.9	90–100	89
	125°	30 min.	9.0	100	205
	120°	1	9.0	100	135
B_2	125°	3	9.0	0	205
	120°	1	9.0	0	135
	90–100°	2	5.0	0	145
	25°	24	0.05–0.10	0	170
	119°	4	2.5	0–10	146
	25°	10 days	9.5–10.0	30	145
	98–100°	2	8.3	50	145
	123°	4–5	5.0	50	145
	123°	4–5	3.0	50	145
	122–125°	4–5	8.3–10	75–100	145
	120–125°	4	10.0	100	147
	119°	4	9.6–10.3	100	146
B_3	20°	1–5 days	Alkaline	10–40	150
	120°	1	6.0	50	135
	60°	1–5 days	Neutral	100	150
B_4	120°	1	9.0	100	135
y	120–125°	4	9.0–10.0	0	147
C	25°	14 months	1.6–2.2	0	186

Northrop (38) found that pepsin in solution at 38° C. attained an optimum stability at p_H 5.0 with slow destruction occurring at lower p_H values and very rapid destruction at higher p_H values. The inactivation of the pepsin was not reversible. Loughlin (277) claimed that the rate of heat-inactivation of pepsin was a minimum and was almost constant within the p_H range 3–4.5. Vahlteich (93) stated that Elixir of Pepsin of the N. F. formula deteriorated 100% during 2 years, but when no hydrochloric acid was added the elixir deteriorated only 36% in the same period of time. The author stated that the p_H of the elixirs which lost their entire activity was close to the optimum p_H for peptic digestion (p_H 1.2–1.6).

Pace (172) reported the optimum p_H for trypsin stability as p_H 6.5. The optimum p_H for trypsin activity is 7.5–8.3. McGillivray (166) reported the optimum p_H for the thermal stability of pancreatic lipase as p_H 6.0. The optimum p_H for lipase activity varies from 5.0–8 5, depending on the source.

(*To be continued.*)

THE CHEMISTRY OF THE HORMONES.

Under above title the *Journal of the American Medical Association* (March 30th) states:

"Although the question of the chemical nature of the hormones has been a subject of interest for nearly two decades, progress in this field has been exceedingly difficult because of the lack of endocrine preparations of sufficient purity for accurate chemical studies. Recent extensive investigation, however, has led to vastly improved methods of preparation and ultimately to the isolation in pure crystalline form of a number of the hormones. Thus these heretofore inaccessible substances have been brought within the scope of attack by the chemist. Indeed, at present several hormones have been prepared in crystalline form and the chemical structure and method of synthesis of two of these have been definitely established. Also a number of other hormones have been prepared in a highly purified although noncrystalline state, and some information regarding their chemical properties has been obtained."

THE DEPARTMENT OF THE AMERICAN ASSOCIATION OF COLLEGES OF PHARMACY

C. B. JORDAN—CHAIRMAN OF EXECUTIVE COMMITTEE, A. A. C. P., EDITOR OF THIS DEPARTMENT.

Habitat learned by "brute memory" is easily forgotten while habitat associated with geography, history and travel will be easily learned and not easily forgotten. Dr. Wirth has presented, in the following paper, excellent suggestions for associating drugs with geographical locations. Such suggestion followed and expanded will add interest and pleasure to the teaching of a phase of pharmacognosy that can easily become burdensome.—C. B. JORDAN, *Editor*.

THE TEACHING OF HABITATS IN PHARMACOGNOSY.*

BY ELMER H. WIRTH.[1]

In the learning of habitats the average student associates with the name of the drug, the name of a geographical locality; a name having some familiarity perhaps, but which in the end means nothing more than just another name for him to memorize. These facts, however, must be learned and in some cases "brute memory" seems the only solution. Yet, in many cases, we may perhaps find methods of association which will not only ease the student's burden, but will create within him a desire to think. And after all the thinking student will be a far greater credit to his profession than the one who has learned "a la parrot fashion."

In the teaching of habitats such desirable association may be created. The best way perhaps involves the instillation of some geographical knowledge along with the discussion of the drug. This after all is not a difficult task as most students display considerable interest in information concerning foreign lands. It can be done in three ways: *First*, by accounts of the history, collection and commerce of the drug, with mention of the topography and the locality of the region where it is found or cultivated. If the drug is one mentioned in the Bible, the Travels of Marco Polo, or other historical or travel work, familiar to the student, his interest is automatically excited. A second way involves the use of pictures. This brings into play a visual aspect of what was expressed above. The free use of photographs, or preferably lantern slides, in illustrating accounts of the commerce of drugs makes an invaluable combination.

A third way concerns maps. The drug map represents a more or less extended geographical area and presents a collective picture of the traffic in drugs. It has been our experience that considerable may be accomplished with maps. The Pharmacognosy Museum contains an habitat case holding some two hundred samples of crude drugs, each sample being attached by means of a streamer to its locality on a large world map. Various other cases in the museum contain small maps illustrating particular features in the traffic of the drugs displayed.

Our laboratory manual in Pharmacognosy is of the loose leaf type to facilitate its being combined with the laboratory notes and drawings. Into this manual we have inserted six outline continent maps, corresponding in size to the pages of

* Parts of a paper read before Teachers' Conferences, A. A. C. P., Washington meeting, 1934.

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the manual. The continent maps are preferable to a single world map in that crowding is eliminated. As each drug is considered its habitat is briefly discussed, taking into consideration the country yielding it together with its cultivation and commerce. The student enters the habitat in his notes, at the same time indicating its location by printing or writing the name of the drug on the proper map.

This method at once accomplishes several things. The maps give the student a graphical picture of pharmacognostical and ecological distribution over the various parts of the earth. His interest in geography is renewed as he sees its connection with other divisions of learning, particularly his chosen profession. He begins to accept a collective picture in which several relationships are orientated. His general knowledge is increased. His interest is stimulated. And finally, he retains his habitats with much less effort because he has diverged from the forceful mechanical association of terms which mean little more to him than combinations of letters, to a logical method of proper association.

The question naturally arises as to the value of habitats. They comprise but a minor part of pharmacognostical instruction and undue stress should not be placed upon them, especially at the expense of other more valuable instruction, yet, as has been explained, they offer a link in the association between pharmacognostical and other knowledge. They comprise, therefore, a division which the teacher should not overlook, in his effort to create interest in his subject. After all, when pharmacy goes before the public annually during Pharmacy Week, what is the center upon which the great majority of displays are built? The drug map.

Should students who have not had a thorough course in physiological chemistry be taught one phase of it, such as urinalysis? To-day the physician is not satisfied with urinalysis alone, but he usually wishes a more complete analysis involving blood analysis, gastric analysis, etc. However, there is still perhaps a demand in certain localities for the pharmacist who is able to do simple urinalysis. If so, then such a course should be offered in the college of pharmacy. The following paper by Professor Greene and a discussion by Professor Gershenfeld will be of special interest to the instructor who is called upon to offer a course in urinalysis.—C. B. JORDAN, *Editor*.

TEACHING URINALYSIS TO STUDENTS OF PHARMACY.

BY ANTOINE E. GREENE.*

Perhaps this paper should be prefaced with an apology. If the present and future curricula in pharmacy are to be governed by the stern mandates of the Fourth Edition of the Pharmaceutical Syllabus, there will be no place for a course in Urinalysis, and this paper will be but a reflection of the ancient history of the subject.

It is the prayerful purpose of this paper to utter a protest, to enter an appeal. There is always the fundamental need for the consideration of local situations. In this period of tremendous transition in our education methods, we should be governed by the rule of curricular elasticity. While, in the main, we should attempt a firm adherence to unified basic and professional subjects, we should have open minds to receive and understand a "theory of elasticity" in the setting up of elective

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courses for our student body. Cast iron courses in a cast iron curriculum, with little chance for change or diversion, for student participation or interest in the choice of electives, are to be deplored. These straight and narrow curricula sterilize the students' interest, enthusiasm and ambition. It is our high hope that urinalysis remain as an acceptable elective, perhaps fortified if possible by the addition of blood chemistry, to become the equivalent in hours and credit of the course in biochemistry as outlined in the current syllabus.

In our course we attempt to acquaint the student thoroughly with the modern technique involved in the routine examination of normal and pathological urines. The student learns by doing. He examines his own urine to acquaint himself with a normal urine picture. The instructor examines each student's urine to determine whether or not the urine is normal, for now and then, a case of an abnormal urine is discovered.

The preparation of diagnostic reagents for the use of physicians is emphasized. Since many physicians conduct chemical examinations of urine in their office laboratories, we feel that the pharmacist should be prepared to furnish the busy practitioner with those reagents which he needs and frequently calls for.

In those qualitative tests, where a reaction has a known chemical explanation, such chemistry is brought to the attention of the student by pointed illustration. Where possible, the reasons for adding this and that, and the explanation of the resulting color or precipitation are carefully outlined and elucidated. Each student is urged to make use of the library facilities, and the use of modern textbooks and journals is encouraged for there are assignments which can only be completed outside of class.

From the normal urine, the student is led to the examination of abnormal specimens. Samples of pathological urines are obtained from the laboratory of an associated hospital, and, occasionally, private physicians submit specimens for both qualitative and quantitative examination. Time does not permit any extensive consideration of microscopic or bacteriological urinalysis. It is the purpose of the course to ground the student in the chemical examination of urine, and to do that well.

While our classes are made up of students who have had preliminary courses in the biological sciences, we review in lecture the anatomy and physiology of the excretory system and briefly touch upon the metabolism of the fats, carbohydrates and proteins in the human body in order that biological activities be understood from the viewpoint of interpretative urinalysis.

While the class meets for sixteen didactic hours and sixteen 3-hour laboratory periods per semester, by rotation of samples, each student examines at least one hundred specimens. We consider it a good practice to have the students check each other's results. This makes for a wholesome rivalry. Some students bring in samples of the urines of their friends, and delight to "diagnose" the ailments of their friends. The first we encourage; the second, we condemn. The function of the lay analyst of urine is to report findings, not to diagnose disease.

There is also a good-natured rivalry with the medical students who are studying physiology and physiological chemistry, and it may be honestly said that our students in pharmacy possess a better understanding of the technique of urinalysis than their fellow students in medicine. In fact, we have had several medical students elect our course as a foundation for future work in junior pathology. Several of our graduates have written to the college wishing to pursue such work as we now give in urinalysis, although appending a desire for comprehensive instruction in blood chemistry.

We attempt to inject the elements of interest in the course from the very beginning. As our students check in their desks, we have them take an actual inventory of the supplies and materials furnished them. This gives them an appreciation of the approximate cost of the necessary apparatus for setting up their own laboratories. The cost of preparing diagnostic reagents is also estimated, so that the student may compare the actual cost of preparation with the list price charged by commercial firms. This, we believe, vitalizes the subject with an added interest. The student is inspired with the idea that he may capitalize his professional knowledge by meeting the professional demands of the medical practitioner. And so it should be.

If, in the new order of things, the young medical practitioner comes to realize that his fellow

pharmacy graduates in the after-graduation era can aid him in the service of the public health, an *entente cordiale* will be established for the mutual good of medicine and pharmacy.

Perhaps we may be deluded, but our students manifest an enthusiasm for the work which is most gratifying when many of the major and required courses are considered by them to be necessary evils along the scholastic path to a diploma.

A case in point might well be related. One student found that his urine contained a large amount of indican. He admitted to irregularity and a heavy protein diet. From this diet he changed to a vegetable diet containing much roughage. Evidently his experiment must have been very successful, for not only did his indicanuria disappear, but his entire physical appearance changed for the better. Often during the stress and uncertainty of examination time, we come across an emotional glycosuria. And with many other conditions of physical and psychic stress and strain we uncover temporary abnormalities by way of urinalysis. These cases are interesting as they point out conditions discussed in the lectures and recitations.

Some students exhibit a desire for the more advanced laboratory methods connected with the clinical analysis of urine. These students are assigned *first*, to library research, and *second*, the preparation of the more delicate reagents. Where possible, these students are given individual instruction in the use and care of instruments of precision employed in urinalysis. It is our policy to allow these students to prepare the reagents in quantity which are to be used by the class. Special meetings are held when discussion of any question pertaining to the subject matter of the course may be entered in by students and members of the faculty. We call these conferences—symposia, and they are most interesting and valuable to all those who attend and take part in them.

In our experience we have found two or three interested students who were fitted for these advanced assignments, and it has been our policy to encourage to the fullest extent such interest by a personal participation in the student's problems. In all work of this kind, we lay emphasis upon integrity, patience and accuracy.

It has often been said facetiously that a difficult test in a clinical laboratory examination becomes a "sink test." That slur upon the laboratorians of our hospitals is slowly dying the deserved death of unrighteous error. In the future, it will be forgotten because of the honest and efficient service of a group of trained men and women, wholly devoted to honest and efficient laboratory analysis as a fundamental and necessary aid to the diagnosis, treatment and prevention of disease.

If it could be possibly arranged, a well-constructed course in clinical laboratory methods might well be substituted for the present optional course in biochemistry as outlined in the syllabus. This course should be carefully organized, with a view to pointing the lectures and recitations to the utilization of facts in the laboratory. This course should consist of lectures, recitation, conferences and laboratory periods to be equivalent to the number of hours assigned to biochemistry and to receive equal semester hour credit. Blood chemistry, as well as urinalysis should be included in the laboratory schedule. The lectures could be so formulated as to include those essential phases of biochemistry of particular value to the content of instruction. This course to consist of 32 didactic and 96 laboratory hours would be an elective to be chosen by those pharmaceutical, medical and special students who had the necessary preparation in the basic chemical and biological sciences.

The writer wishes to give an outline of the course as given at present, with a sample examination based upon the lectures, recitations and laboratory work.

1. The Definition and Classification of Urine Examinations.
   1. Physical. 2. Chemical. 3. Microscopic. 4. Bacteriological. 5. Clinical.
2. The Normal Urine Picture.
3. The Pathological Constituents of Urine.
4. Glossary of Terms.
5. Qualitative Examination of a Normal Urine for: Indican; Creatinine; Dextrose; Urea; Uric Acid; Bile; Blood; Acetone; Diacetic Acid; Chloride; Sulphate; Phosphate.
6. Qualitative Examination of a Pathological Urine for: Glucose, Creatinine, Blood, Bile, Uric Acid, Indican, Acetone, Diacetic Acid.
7. Eight Tests for Reducing Sugar, Differentiation of Glucose, Levulose, Lactose and Pentose.

8. Eight Tests for Urinary Albumin.
9. Quantitative Examination of Urine for Urea:

1. By Hypobromite Method. 2. By Urease Method.

Ammonia:

1. By Schiff-Malfatti Method. 2. By Aeration Method.

Chlorides:

1. By Mohr's Method. 2. By Arnold-Volhard's Method.

10. Total Sulphates. Total Solids. Total Acidity (by Folin's Method). Ethereal Sulphates.
11. Qualitative and Quantitative Examination of a Sample of Pathological Urine for: Blood, Bile, Acetone, Sugar, Albumin, Diacetic Acid, Total Acidity, Indican, Chlorides, Urea, Uric Acid, Total Solids, Total Nitrogen.
12. Collection and Preservation of Specimens—Refrigeration; Toluene, Chloroform, Thymol, etc.
13. Clarification and Decolorization of Specimens: Talcum, Pumice Stone, Magnesium Carbonate, Lead Acetate, Potassium Permanganate, etc.
14. The Form of Report. 15. Questions and Problems.

EXAMINATION IN URINALYSIS FOR PHARMACY STUDENTS.

1. Outline the normal urine picture.
2. What is the significance of a 24-hour urinary output of 4000 cc. with a specific gravity of 1.035? 3. Calculate the total solids in the above sample.
4. How would you definitely detect glucose in a sample of urine?
5. Briefly give three tests for urinary albumin.
6. What is the composition of: Esbach's Reagent? Benedict's Solution? Obermayer's Reagent? Fehling's Reagent?
7. How could you determine the amount of urea in urine?
8. Give a test for bile in the urine. 9. How would you clarify a turbid urine?
10. Give the test for urinary indican, and the chemistry involved.

Those who sit for these lectures, who work in the laboratory on many samples, and who pass successfully the examinations given at the end of the course, are fit, we believe, to begin a more advanced excursion into the field of clinical chemistry.

Although we may have been unduly negligent of our responsibilities, there comes to us a great comfort, even in our feeling of uncertainty as to the real value of our efforts in teaching a depised and rejected subject.

Comes to us the poignant realization that on the front lines of the public health defensive, there are young men and women working quietly and efficiently in the hospital laboratories in the service of medicine as it ministers to the needs of an underhospitalized and underprivileged minority. These servants of the national health received some little training in urinalysis at our hands. Our task in teaching goes on.

COMMENTS ON PAPER BY PROFESSOR ANTOINE E. GREENE ON "TEACHING URINALYSIS TO STUDENTS OF PHARMACY."

BY LOUIS GERSHENFELD.*

It is difficult to offer a critical discussion of instruction of the kind you have just received from Professor Greene. To do justice to the subject would require more time than is at our disposal. It is, however, possible to offer certain suggestions and even to ask a question or two in the hope of all of us receiving more instruction.

* Professor of Bacteriology and Hygiene and Director of the Bacteriological and Clinical Chemistry Laboratories at the Philadelphia College of Pharmacy & Science.

I have been and am deeply interested in the subject which has been reviewed. The retail pharmacist to-day falls into several classes. In a rural and suburban store, the pharmacist must have a knowledge of horticulture, agriculture, first aid; and he serves best if he is capable of assisting the medical practitioner at all times, and this includes service as a laboratory technician. In small hospitals, pharmacists are frequently required to help as technicians in the laboratory. There are those students in pharmacy who after the first few years of study enjoy and therefore feel that they are especially qualified in laboratory work, and prefer to train themselves along these lines. Even in urban stores, especially where professional pharmacy is practiced, the clinical laboratory and especially the accurate performance of urinalyses can be of great service to pharmacy and the medical practitioner. In brief, we must admit that this is an age of specialization, and the pharmacy student who at the end of his career wants to be qualified for certain duties which fit in with the practice of pharmacy should be granted that privilege. Our courses in pharmacy must meet the demands of such branches of study as fit in with the practice of professional pharmacy, and elective courses in the curricula will help this situation very much. I am in full accord with the suggestion of Professor Greene that urinalyses be an acceptable elective and if possible a required subject of study, and preferably fortified by other commonly performed clinical laboratory tests. This will fit in with the Applied Bacteriology and Public Health Studies, which are required subjects as outlined in the Pharmaceutical Syllabus, fourth edition. We find, of course, listed in the latter Bio-chemistry, which is included as an optional subject and herein is to be found a consideration of excretions including urine. It is much more desirable to arrange for a thorough course in urinalysis and other clinical laboratory methods. At our own institution we are giving the latter as a required subject.

Professor Greene's comment is well taken that pharmacists should be prepared to dispense diagnostic reagents. These may be requested by the practitioner, who does his own laboratory work; and in some instances the laity may make inquiries for such preparations. It is not uncommon to find diabetics (especially those using insulin) testing their own samples of urine qualitatively for sugar, having received this instruction from their own medical attendants. Such patients don't understand why pharmacists cannot supply Benedict's solution or other reagents. How many drug stores stock litmus paper frequently requested by customers? Many instances could be cited where contacts with medical practitioners were made due to the pharmacist's ability in supplying a diagnostic reagent.

Professor Greene states that "It is the purpose of the course to ground the student in the chemical examination of urine and to do that well." And he further states: "Time does not permit any extensive consideration of microscopic or bacteriological urinalysis." Inasmuch as the title of this paper is "Teaching Urinalysis to Students of Pharmacy," it seems to me that it is important to direct attention to the fact that a careful microscopic study must be made a part of this instruction, and as much emphasis should be made upon the value of the microscopic findings as upon the chemical findings. A bacteriological examination is conducted only occasionally but a microscopic examination is and must be at all times part of a routine urinalysis. Despite a most careful chemical examination with or without the finding of abnormal (chemical) constituents, a correct interpretation of these chemical findings or the possibility of such urinalyses serving as an aid in diagnosis or prognosis may also necessitate microscopical laboratory aid. A careful microscopic examination should be part of every routine examination and in my own observation and experience, I have found that it is most desirable to give the chemical and microscopical instruction either at the same time or during the same semester. If possible, the same instructor may handle both phases of this study, or if need be the microscopical and chemical departments may cooperate. Even in many of the medical schools, there is a lack of proper coördination in the instruction as it is presented when the chemical and microscopic examinations of urine are given to the undergraduates. There may even be too much emphasis given to the chemical examination or too little to the microscopic examination. Frequently the medical student is not in a position to learn the interpretation of the combined findings until he is assigned to the laboratory during his internship. In some measure this may account for the fact that entirely too many practitioners who do their own urinalyses merely do the chemical examination and do not carry out a microscopical examination, even though many of them have microscopes. Many examples could be cited to illustrate the above points. There may be albumin found in the sample. This may or may not be of marked significance depending upon the microscopical findings. It is a frequent

occurrence during the warm weather to find samples in transit and not properly preserved revealing an abundant quantity of bacteria, most of which developed after the collection of the sample. During transit, it is possible for sufficient albumin to be extracted from the abundant growth of bacteria to give a positive chemical test for albumin. Also there are several chemical entities recognized microscopically by their characteristic type of crystals. Uric acid, triple phosphates, calcium oxalate, leucine, tyrosine and cystine are examples of some crystals which are revealed microscopically and are not detected chemically in urine as tests are not conducted for these in the routine chemical examination. We have fallen into the habit of speaking about the chemical test for blood, but you all know that it is in reality a chemical test for hemoglobin; so that this chemical test does not reveal whether we are dealing with a hemoglobinuria (only hemoglobin in the urine) or a hematuria (whole blood in the urine). The latter denotes a pathological condition of the genito-urinary tract, while a hemoglobinuria is in most instances the result of abnormalities outside of the genito-urinary tract. Whole blood (as found in hematuria) will be revealed not only by a positive chemical test (for hemoglobin), but also by the finding of unruptured red corpuscles microscopically. Pus cells, casts, mucus and other organized cellular elements and evidences indicating disease of the urinary tract may be found upon microscopic examination, when a chemical examination may reveal no abnormalities. Let us remember that if there is some faulty arrangement in the instruction and in the lack of the coördination of the various phases of urinalyses as given to medical students, the latter have the added advantage of additional training in a hospital during internship. The pharmacy student does not have and may not receive this added advantage and we who are responsible for seeing that such students are in a position to aid the medical practitioner must be assured that they will do so to the maximum degree.

I agree with Professor Greene that the worker must only report and not attempt to interpret laboratory findings. But at the same time he must be possessed of a rich fund of knowledge not so much to aid in interpreting the findings or to give information as to collection, preservation, etc., when such assistance and information are requested by the practitioner (who makes available other facts which are needed), but mainly because of the fact that the laboratory worker will be in a more favorable position to apply such better judgment in reading the findings revealed after the performance of the laboratory tests.

I think we all agree that it is a difficult task to include all data concerning urine in any course. At the same time an orderly arrangement of the whole subject should be maintained. Though many techniques should be given for the qualitative and even quantitative examination of various constituents, the instructor should point out the relative value of the different procedures and the practical importance of the knowledge resulting therefrom. There are many techniques used in hospital laboratories or by Insurance Company examiners when testing samples of urine that are satisfactory for clinical purposes but which would not answer for research study. Yet these are the methods of choice in clinical laboratory practice and it is advisable to consider them. May I add a few additional notations to the outline of Professor Greene on the course as suggested by him, the inclusion of which will be helpful:

1. A consideration of the frequency of urination and volume voided and factors influencing the latter.
2. It is assumed, I believe, that the physical examination is to include a consideration of transparency and sediments; odor; coloration and pigments; reaction; specific gravity; and the methods employed to report these findings.
3. Mention is made of tests for urinary albumin. This I assume is to include also a consideration of Bence-Jones protein and proteoses, nucleoprotein, etc.
4. Tests for Bile are to include methods for Bile Pigments and Bile Acid Salts.
5. Mention should be made of the Diazo Substance and the Diazo Reaction, a test still requested by some.
6. Detection of Inorganic Metallic Poisons in Urine as arsenic, lead, mercury, etc., should be included as this is becoming of greater significance in pathological conditions.
7. A consideration of tests for kidney function should be given, especially mentioning the technique of the Phthalein or Vital Red Test, as frequently the samples of urine are sent to the laboratory worker who is requested to determine the quantity of phenolsulphonephthalein eliminated.

PROCEEDINGS OF THE LOCAL BRANCHES

"All papers presented to the Association and Branches shall become the property of the Association with the understanding that they are not to be published in any other publication prior to their publication in those of the Association, except with the consent of the Council." —Part of Chapter VI, Article VI of the By-Laws.

ARTICLE III of Chapter VII reads: "The objects and aims of local branches of this Association shall be the same as set forth in ARTICLE I of the Constitution of this body, *and the acts of local branches shall in no way commit or bind this Association, and can only serve as recommendations to it.* And no local branch shall enact any article of Constitution or By-Law to conflict with the Constitution or By-Laws of this Association."

ARTICLE IV of Chapter VII reads: "Each local branch having not less than 50 dues-paid members of the Association, holding not less than six meetings annually with an attendance of not less than 9 members at each meeting, and the proceedings of which shall have been submitted to the JOURNAL for publication, may elect one representative to the House of Delegates."

Reports of the meeting of the Local Branches shall be mailed to the Editor on the day following the meeting, if possible. Minutes should be typewritten with wide spaces between the lines. Care should be taken to give proper names correctly and manuscript should be signed by the reporter.

BALTIMORE.

The April meeting of the Baltimore Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held at the Hotel Emerson on Monday, April 29th, President Reindollar presiding.

The meeting was preceded by an informal dinner in honor of the guest speaker, Dr. Walter H. Hartung; ten members and their guests were present at the dinner.

The minutes of the March meeting were read by the secretary and approved. President Reindollar then introduced the speaker of the evening, Dr. Walter H. Hartung, director of Research, Sharp & Dohme of Philadelphia.

Dr. Hartung selected for his topic, "Iatrochemistry and Pharmacy in 1935." He stated that in 1935 the old term iatrochemist should be revised to include chemists who are studying the influence of chemical structure upon physiological activity. In a study made several years ago, it was pointed out while the U. S. P. V had only three synthetic drugs the present Pharmacopœia recognizes 130 such compounds. Dr. Hartung pointed out also that many of our most valuable drugs used as antiseptics and anesthetics are pure synthetic compounds.

After an historical review of his topic Dr. Hartung described in detail the interesting work that is going forward in his laboratory on studies of derivatives of propriophenone. During the course of his lecture the speaker elaborated on his discussions by explaining the reactions involved and the structural relationships of the various compounds. He described the first pressor anesthetic as developed in his laboratory and showed the interesting fact that the meta OH group in epinephrine is more important than the para OH group.

Dr. Hartung concluded his talk by discussing the iatrochemistry of mescaline and pointing out recent developments in the study of the sex hormones. Finally a plea was made for a better understanding between the pharmacologist, the chemist and the physician in the clinic.

At the conclusion of the address a general discussion was entered into by the members present. President Reindollar extended the thanks of the organization and called for a rising vote of thanks. About twenty-five attended the meeting. The meetings of the Branch were called off until Fall.

C. JELLEFF CARR, *Secretary-Treasurer.*

NEW YORK.

The April meeting of the New York Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on April 8, 1935, in the New York College of Pharmacy, Columbia University. About eighty-five members and their guests attended.

After the meeting had been called to order by President Charles W. Ballard, the secretary was called upon for his report which was read and accepted. The treasurer, Mr. Turner F. Currens, reported a balance on hand.

Chairman Lehman of the Committee on Education and Legislation, then reported as follows:

Federal Legislation.—N. I. R. A., Senator Pat Harrison's Bill S. 2445 on Code Legislation, gives the following powers to the President of the U. S. in tentative draft of Revised N. I. R. A.

1. To establish rules of fair competition.
2. To promote or maintain coöperative organization and action of trade and industrial groups.
3. To induce or maintain coöperative relations between, or coöperative activities of, labor and management.
4. Promote or maintain fair competition.
5. Prevent or eliminate competitive practices which are unfair or destructive of fair competition, or restraints upon trade which tend to diminish the amount thereof contrary to the public interest.
6. Promote the fullest effective utilization of the productive and distributive capacity of trade and industry.
7. To prevent or eliminate restrictions upon production, except those hereinafter expressly sanctioned.
8. Promote or maintain increased purchasing power and increased consumption of industrial and agricultural products.
9. Reduce or relieve unemployment or regularize employment.
10. To establish proper minimum wages and maximum hours of labor.
11. Improve the standards and conditions of labor.
12. Promote the rehabilitation of industry.
13. Conserve natural resources and prevent production or competition wasteful of such resources, and injurious to, commerce therein.
14. To remove unreasonable burden upon or protect the reasonable flow of interstate or foreign commerce.

The bill in question refers, however, to interstate and foreign commerce.

It is claimed that the amended law is a tactical admission that most of the Fair Trade provisions in the present Code are unconstitutional. (Mr. Richberg is given credit for having written this bill.)

There are several Anti-Price Discrimination bills before Congress—Mapes Bill, H. R. 5062, Wheeler Bill S. 944, Bankhead Bill S. 2211, Huddleston Bill, H.R. 6618, White Bill, H. R. 6246.

These bills would make it unlawful to discriminate in price of any commodity, regardless of quantity purchased at wholesale.

The King Bill S. 1923 would legalize reasonable written trade agreements for the regulation of competition: similar to the Capper-Kelly Bills.

All of these have the support of retail trade organizations, and are an evidence that our lawmakers are beginning to realize that something must be done to save the small distributor.

The Black 30-hour bill would limit the working hours in commercial and manufacturing establishments to 30 hours weekly; the bill has been reported out of committee favorably and is on the calendar. It is on the Senate calendar for action. It is opposed by commercial and industrial bodies.

There is a possibility of the Copeland Pure Food, Drugs and Cosmetics Bill S. 5 coming up for action soon. There are still many objections to the same from various sources which will make enactment difficult.

I have here a protest issued by the National Committee of Manufacturers of Cosmetics, objecting to certain regulations as to the labeling of antiseptics.

So far, five states besides California have enacted the Fair Trade Law (Junior Capper-Kelly Bill), namely, New Jersey, Washington, Oregon, Maryland and Arizona. The Committee on Legislation of the N. Y. State Pharmaceutical Association is making strenuous efforts to have our bill passed this session of the Legislature: the bill is to come up for vote to-day, April 8th. Send telegrams to Senator Dunnigan and to the Assemblyman and Senator of your own district, favoring the passage of the bill.

State Legislation.— The Assembly has passed the Prophylactic Bill (Stewart int. 489) and sent the same to the Senate for action on April 3rd.

Delay in legislative action has been due to the rivalry of two Democratic factions in the Metropolitan district in the question of reapportionment: also there has been powerful opposition to the Fair Trade bill from department store and price cutter organizations.

The N. Y. Pharmaceutical Council has protested against the raids being made by the Federal Alcohol Tax Unit on drug stores in which it is alleged that untaxed alcohol was found; telegrams were sent to John T. Flynn, supervisor of the Alcohol Tax Unit, Secretary of the Treasury, Morgenthau, and Rowland Jones, Washington Representative of the N. A. R. D.

Chairman Cosmo Ligorio, of the Membership Committee, submitted the association membership application of Mr. Stummer for forwarding to Secretary Kelly.

Fred Schaefer reported that the question of branch affiliation had been considered thoroughly and that there was no provision which would prevent the Branch from affiliating with the State Association or with the newly organized Council. He, therefore, moved that the Branch become affiliated with the State Association and that it should appoint two permanent delegates to the New York Pharmaceutical Council, and appropriate $10.00 for each delegate; the sum of $20.00 to be paid to the New York Pharmaceutical Council. The secretary asked Mr. Schaefer if affiliation would obligate the Branch to have one-half of its membership, members of the State Association. In answer to this, Mr. Schaefer stated that the State Association did have such a requirement for pharmaceutical organizations affiliated with it, but that it would forego this provision and follow a new procedure, of one delegate for the first twenty-five state association members and one for each fifty additional state association members during the period 1935. In 1936, the requirement would be one delegate for every twenty-five state association members. Since there was no further discussion a vote was called and the motion was approved.

Dr. Hugo Schaefer then submitted the framed life membership certificate given to Dr. Fischelis at the time of his recent testimonial dinner. This was received by the Branch for forwarding to Dr. Fischelis.

President Ballard announced that Dr. Fischelis, president of the AMERICAN PHARMACEUTICAL ASSOCIATION, would address the Branch at its meeting in May and would elaborate on his ideas for consolidating pharmaceutical organizations.

A letter announcing the testimonial dinner to be tendered Dr. Ernest Little on May 20th, was read by the secretary. In commenting upon this, Dr. Ballard urged the members of the New York Branch to coöperate. Dr. Hugo Schaefer suggested that a brief announcement of this dinner be included in the New York Branch meeting notice for the May meeting and also proposed that the New York Branch should try to at least make up one table, if not more. He also urged close coöperation with the Northern New Jersey Branch.

The application for Branch membership of Prof. Peter Conroy was received and favorably voted upon.

Secretary Hugo Schaefer, of the Remington Medal Committee, then announced that the Remington Medal for 1935 had been awarded to Samuel Hilton, well-known retail pharmacist and association worker, of Washington, D. C. The secretary was directed to write him a letter of congratulations.

No specific plans for the presentation of the medal were discussed and it was suggested that the matter be taken up by the Executive Committee of the Branch.

Chairman Leonard Steiger, of the Committee on Progress of Pharmacy, was then called upon for his report which follows:

The *Chemist and Druggist* (London 3/23/35) reports on the discovery of a new Ergot alkaloid by Dudley and Moir of the National Institute for Medical Research. It has been named "Ergometrine" and it is found in the B. P. liquid extract of Ergot. In the author's opinion the isolation of Ergometrine indicates that the substance for which ergot was actually introduced into medicine, has been obtained. For oral administration ergometrine is described as the essential constituent of ergot extracts.

(*Ind. Eng. Chem., News Ed.*, Vol. 13, No. 7, 4/10, 1935.) The first Eli Lilly award in Biochemistry goes to Wm. N. Allen of the School of Medicine and Dentistry of the University of Rochester. The basis of the award is the outstanding work done by Dr. Allen in developing a sharply defined biological test for the action of *Corpus Luteum*, the use of this test to isolate a po-

tent extract, and the complete purification of the hormone, "progestin." The present knowledge of the solubilities and physical characteristics of progestin is due to the work of Dr. Allen, who, with R. K. Meyer, achieved the first separation of "progestin" from œstrin.

Thomas N. Fraser in *British Medical Journal* (1934) reports on a fatal case of subacute yellow atrophy of the liver after use of cinchophen. On account of its toxicity the advisability of abandonment of the administration of cinchophen is considered.

Very successful treatment of severe mushroom poisoning with large doses of coramine (*Med. Klin.*, 1934, rep. by *C. A.*, Vol. 29, 1505). Cases of mushroom poisoning in which among other symptoms loss of consciousness, cyanosis and severe respiratory depression have occurred, have responded remarkably to treatment with large doses of coramine. It has been used very successfully also in cases of respiratory depression and failure, during anesthesia poisoning with narcotics and so forth.

Following Mr. Steiger's report, Dr. Ballard introduced the speaker of the evening, Dr. Arno Viehoever, professor at the Philadelphia College of Pharmacy and Science who spoke on "Evaluation of Cathartic Drugs."

Dr. Viehoever's address centered about the use of a new test animal for biological standardizations. This small test animal, Daphnia, possesses numerous advantages which make its use as a biological test animal particularly advantageous.

The extremely interesting and instructive moving pictures showing the effects of strychnine on the test animal proved ample evidence of the one great advantage, namely, the transparency of the animal.

The lecture included numerous demonstrations and lantern slides which added very considerably to the interest of Dr. Viehoever's address.

The adaptability of the test animal for standardizing drugs of the anthraquinone series such as senna, frangula, rhubarb, cascara and aloe was very well shown in the moving picture films which Dr. Viehoever presented.

Dr. Viehoever answered questions relative to the subject. He was given a rising vote of thanks.

RUDOLF OTTO HAUCK, *Secretary.*

NORTHERN OHIO.

The April meeting of the Northern Ohio Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on the evening of April 12, 1935, at the Faculty Club of Western Reserve University, Cleveland. About forty members and their friends attended.

President Speer called the meeting to order and the report of the secretary was read and approved.

Dr. Lawrence P. Hall, of the research staff of the Mallinckrodt Chemical Works, St. Louis, was then introduced. By means of lantern slides and considerable demonstrating material and interesting specimens, Dr. Hall treated the Branch to a very much worth-while discussion of the uses of bismuth and its compounds. Some of the high lights of the discussion follow:

Because bismuth is in daily use, we are apt to forget that it is not a common element, but actually one of the rarer elements. It is present in the earth's crust to the extent of about one part in ten million.

The bismuth consumed in the world amounts to around 400 tons per year and is obtained from Peru, other South American countries, United States, Canada, China, Australia, etc. The domestic supplies are obtained primarily as a by-product from lead refining. The metal produced in this way is of high purity.

When combined with pure chemicals by properly controlled processes, this metal permits the production of pure compounds. The most common ones are the subcarbonate, subnitrate, subsalicylate and subgallate, although various other salts are used, such as the oxychloride, betanaphtholate, subiodide, various organic derivatives such as tartrates, etc.

Bismuth and its compounds have certain peculiar properties which make it desirable for use in industry, in the laboratory, in cosmetics, in dentistry, in radiology, and most important of all, in pharmacy. Industrially, bismuth, itself, is widely used in low melting alloys, which find application in safety devices such as sprinkler heads, links for fire doors, plugs for gas cylinders and boilers; in machine shops for bending thin wall tubing, sealing glass to metal, setting and aligning

dies, molding, soldering, etc., in toys, such as trick spoons and casting outfits for children; and in other surprising and constantly increasing uses. Bismuth compounds are used in producing lustre finishes and glazes on dishes, vases and artificial pearls; in glazes for gold; in dense, refractive optical glass; in luminous paints. Probably high cost prevents more extended use.

The cosmetic use dates from the seventeenth century when Lemery made a fortune from the sale of "Magisterium of Bismuth" for face powder. Bismuth salts have excellent covering power and adhesion but are sensitive to discoloration by hydrogen sulphide and are drying to the skin.

In radiology the introduction of bismuth salts for visualization of the gastro-intestinal tract provided the principle for examination of hollow organs of the body. Bismuth compounds have also been used for outlining the bladder, abscesses, fistulas and sinuses.

In medicine, bismuth salts are used topically and systemically. Externally they may be applied as ointment, paste or powder to form a slightly astringent, dry scab which gives mechanical protection and allows rapid healing Internally they form soothing protective coatings, effective in certain gastro intestinal ailments. Systematically various types of bismuth compounds are used hypodermically for syphilis, frambœsia and Vincent's angina.

In these various uses the properties of prime importance to the pharmacist include purity, kind of crystal form, color, light stability, fineness and chemical stability. By way of illustration, some lots of the subcarbonate will turn yellow in light; sometimes improperly prepared subnitrate develops excessive acidity and an odor; coarse material will not give usable suspensions. Bismuth salts which are bulky, finely crystalline, pure and stable should give the optimum benefit in pharmaceutical uses.

N. T. CHAMBERLIN, *Secretary.*

STUDENT BRANCH, ST. JOHN'S UNIVERSITY.

The regular monthly meeting of the St. John's University, Student Branch, of the AMERICAN PHARMACEUTICAL ASSOCIATION was held on March 18th. Preceding the meeting a dinner was held at the Lido Restaurant for the members of the Branch, their friends and guests. The meeting was called to order by President Arancio in the College at 8:30 P.M. The reading of the minutes was suspended in deference to the speakers of the evening.

In announcing the subject for the evening's discussion, "What the Physician and the Professional Pharmacist Expects of the Coming Generation of Pharmacists," President Arancio pointed out that many people see a well-defined trend toward professional pharmacy, away from the ultra commercial type of pharmacy.

It was with the idea of stimulating discussion among the members of the Branch on this important topic that the program of the meeting was arranged. "Bringing to the future pharmacist the viewpoint of the Physician and the Professional Pharmacist in an open forum of this kind should lead to clearer thinking on many of the problems now facing pharmacy, in this shift to a newer type of professional pharmacy of the future," said President Arancio.

Chairman William Matz, of the Committee on Program, after a few introductory remarks presented the first speaker of the evening, Dr. Thomas B. Wood, well-known Brooklyn physician.

Doctor Wood discussed recent advances in the field of medicine and pharmacy, particularly in the field of Endocrine Therapy. In order to meet the needs of the physician, manufacturers had taken it upon themselves to prepare and standardize, either chemically or biologically, endocrine preparations in the form of ampuls for intravenous or subcutaneous use. He asked the question "Can a physician depend upon the modern graduate in pharmacy to prepare an ampul containing a sterile solution of glucose in an intravenous emergency?" It is for this reason that manufacturers have availed themselves of the opportunity to prepare such preparations. Doctor Wood expressed the opinion that pharmacists should be prepared to meet the needs of the physician along these lines. He could do this not only by carrying a full line of preparations for parenteral medication but by being ready, in case of an emergency, to prepare ampuls.

After discussing the evils of substitution and of giving information to the patient regarding the contents or the use of a prescription, Dr. Wood, concluded by stating that the physician expects of the pharmacist of the future: "1. A duly qualified gentleman whose honesty and integrity can be depended upon. 2. To be qualified to prepare special formula tablets and ampuls for intravenous injection, etc. 3. To display the utmost tact in dealing with the patient of the physician. On the other hand the pharmacist should expect of the physician: 1. To adhere, by

and largely to U. S. P. and N. F. preparations in prescribing. 2. To write prescriptions clearly. 3. To expect courtesy from the physician when he phones in regard to an incompatible mixture, overdose, etc."

Dr. Wood expressed the hope that the future will bring a better understanding between physicians and pharmacists in regard to their mutual problems. "Nothing is more noble," said Dr. Wood, "than in aiding in the relief of the sufferer."

Dr. Otto Raubenheimer, well and favorably known Brooklyn Pharmacist was then introduced and spoke on the subject of "What the Professional Pharmacist Expects of the Coming Generation of Pharmacists."

"It is necessary to love your profession," said Dr. Raubenheimer, in pointing out that the practice of pharmacy affords all of the experiences, contacts and conditions necessary for the good life.

In commenting on some of the points covered by the previous speaker, he pointed out the difficulties experienced by local pharmaceutical associations in getting physicians to prescribe U. S. P. and N. F. preparations. The speaker then related many personal experiences he had in dealing with physicians and stressed the necessity for tact as well as professional dignity in dealing with physicians. In connection with the operation of a professional pharmacy, he stressed the essential need for a library adequate to serve the needs of modern dispensing pharmacy.

"The relation between the physician and the pharmacist should be a cordial one and can be made so if each would obligate himself to the ethics of his profession," said Dr. Raubenheimer in conclusion.

After the speakers had answered several questions by the members, a rising vote of thanks was extended the speakers.

ADA J. BIZZARI, *Secretary*

A remarkable gathering of various pharmaceutical interests has always marked the annual A. PH. A. Week, because of the unity and understanding of its membership. The coördination of these elements has made for the success of the annual conventions. The meetings in the different sections of the country have enabled the pharmacists to coöperate for the advancement of American pharmacy.

Prescription Department of L. S. Williams Pharmacy, Baltimore.

ASSOCIATION BUSINESS

AD INTERIM BUSINESS OF THE COUNCIL AMERICAN PHARMACEUTICAL ASSOCIATION, 1934–1935.

Office of the Secretary, 2215 Constitution Avenue, Washington, D. C.

LETTER NO. 14.

March 20, 1935.

To the Members of the Council:

72. Committee on the Proposed Council on Pharmaceutical Practice. Motion No. 24 (Council Letter No. 12, page 166) has been carried and Chairman Cook has been advised.

73. Use of the Text of the N. F. V. Motion No. 25 (Council Letter No. 12, page 166) has been carried, and Mr. Dauer has been advised.

74. Year Books for the Library of Congress. No comments have been received on Motion No. 26 (Council Letter No. 12, page 166) and a vote is called for at this time.

75. Bequest by Dr. Frederick B. Kilmer. President Fischelis has forwarded a copy of the following letter addressed to him by Miss Josephine I. Dooley, Secretary to Dr. Kilmer and an executor of his will:

> Clause 6 of Dr. Frederick B. Kilmer's will recites as follows:
>
> "6. I give and bequeath unto the AMERICAN PHARMACEUTICAL ASSOCIATION, organized under the District of Columbia, the sum of Three Thousand Dollars, to be held in trust, the income to be applied to the awarding of a prize for meritorious work in pharmacognosy, such prize to be known as 'The Kilmer Prize,' or an equivalent designation. In awarding the prize preference to be given to studies in vegetable drugs. The recipient of the prize shall be a graduate in pharmacy. Teachers in colleges of pharmacy, workers in pharmaceutical laboratories, are to be excluded from competing for the prize. Prize to be awarded under such conditions as the ASSOCIATION may elect. Funds arising from the income which may not be used are to be added to the amount of the prize or added to the principal, as the ASSOCIATION may elect."
>
> I give you the above information because it is naturally of interest to your ASSOCIATION. Doctor Kilmer, as you undoubtedly know, died December 28, 1934.

Under the By-Laws of the Council, this communication is referred to the Committee on Property and Funds for recommendation by direction of the chairman of the Council.

76. Report of the Auditor. The following has been submitted:

February 11, 1935.

Mr. C. W. Holten, Treasurer,
AMERICAN PHARMACEUTICAL ASSOCIATION,
Washington, D. C.

Dear Sir:

I have made an examination of the books and accounts of the AMERICAN PHARMACEUTICAL ASSOCIATION and your report, as Treasurer, for the calendar year 1934, and beg to report as follows:

All receipts have been traced to deposits in banks to the credit of the respective funds for which received, and all disbursements have been found evidence by properly authorized voucher checks.

I have verified the cash balance belonging to the various funds, totaling $28,721.36 and found same to be correct.

Investments aggregating a par value of $139,400.00 have been verified by an examination of the bonds representing these securities. All coupons which have not matured as of December 31, 1934 have been found attached to the bonds.

The income account of each of the permanent funds, except the Research Fund, and both of the trust funds have been examined and found to be correct. The income account of the Research Fund fails to include six month's bond interest on $6000.00 U. S. Liberty Bonds amounting to $127.50. The coupons representing this interest were deposited on February 7, 1935.

During the year 1934 a total capital expenditure of $78,590.61 was made on account of the construction costs of the Headquarters Building in Washington increasing the cost of this property to $535,796.07.

Records maintained by the secretary of the ASSOCIATION have been examined and transfers of funds from his account to the account of the Treasurer have been verified.

Respectfully submitted,
(Signed) W. A. JOHNSON,
Certified Public Accountant.

The treasurer's report for 1934 will be printed in a later issue of the JOURNAL as a part of the ASSOCIATION'S records formerly included in the YEAR BOOK.

77. *Sale and Exchange of Liberty Bonds.* Under the Second Call, October 15, 1934, and the Third Call, March 15, 1935, the following Fouth Liberty Loan 4¼% Bonds, 1933–1938, in the funds named, have been called for payment:

Second Call.	October 15, 1934.
Endowment, B-01905922 C	$ 100.00
Centennial, H-04951118 C	100.00
Ebert Prize, 163208 R	1000.00
Research, 30752 R and B-00925702 C	6000.00
Third Call.	**March 15, 1935.**
Endowment, 6605 R	$5000.00
321206 R	500.00
E-00769335 C	1000.00
Centennial, 321207 R	500.00
Ebert Legacy, 364536 R	1000.00
Life Membership, 338207 R	1000.00
364525 R	1000.00
Research, 321205 R	500.00
151885 R	1000.00
Procter, 163207 R	1000.00
365087 R	1000.00
F-01886616 C	100.00

The following letter has been received from Chairman Philip of the Committee on Finance:

Dr. Charles H. LaWall, under date of March 18th, has written me as follows:

"I agree that the capital relieved by the calling in of U. S. Fourth Liberty Loan Bonds owned by the A. PH. A. be reinvested in the U. S. Treasury Bonds of 1955–1960, bearing 2⅞% interest.

Therefore, two of the three members of the Finance Committee approving this exchange of bonds, I ask that you take such steps as are necessary to sell the present bonds and buy the new ones.

If a motion to the Council is necessary for this step, I so move.

This communication answers your letter of March 19th, with enclosure from Henry Morganthau, Jr., Secretary of the Treasury.

There has been called to my attention, the Home Loan Bonds, that pay a better rate of interest. These bonds are, as those favoring the purchase of them express it, 'a moral obligation of our Government.'

It is my opinion that the higher rate of interest, while desirable, should not defer us from considering the greater safety of the bond the Committee suggests purchasing. Security of principle during these trying times for money entrusted to our care is the first and most important consideration."

It will be necessary to transfer two thousand dollars of the accumulated interest in the Life Membership Fund, invested in the above bonds, to the Current Fund.

(*Motion No. 28*) *It is moved by Philip, as Chairman of the Committee on Finance, that the called Fourth Liberty Loan Bonds listed above be sold and that the proceeds be invested in U. S. Treasury Bonds 2¹/₄%, 1955–1960, or that the bonds be exchanged on an even basis, and that since most of the called bonds are registered, and as this form is required, the following be re-adopted* (*see* JOURNAL, A. PH. A., *Dec. 1933, pages 1302–1303*):

> *Resolved, that C. W. Holton, treasurer, and E. F. Kelly, secretary, are hereby authorized to buy, sell, deal in, assign or negotiate the called Fourth Liberty Loan Bonds which are owned by, or registered in the name of, the* AMERICAN PHARMACEUTICAL ASSOCIATION *and to that end, to endorse, transfer and deliver the same.*

By direction of the Chairman of the Council, a vote on this matter is called for at this time, as the exchange cannot be made after March 27, 1935. E. F. KELLY, *Secretary.*

NORTHERN NEW JERSEY BRANCH, A. PH. A.

The Northern New Jersey Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION held its second annual Physician's Night as its April meeting, on April 15th. Due to the development during the year of the New Jersey Formulary the greater part of the evening was devoted to a discussion of this important project. William Richert, of Elizabeth, addressed the physicians and pharmacists on the work from the viewpoint of the pharmacist and Dr. H. B. Wilson, of Hackensack, discussed the physician's views.

Dr. Hans Molitor, director of the Merck Institute of Therapeutic Research, addressed the meeting on the subject, "Therapeutic Research and Its Relation to Pharmacy, Medicine and Chemistry," in which he explained the objects of research in developing new drugs, justifying the use of old drugs, and in developing new uses for old drugs.

SECTION ON PRACTICAL PHARMACY AND DISPENSING.

Due to the fact that the convention date of the ASSOCIATION is in the early part of August instead of the latter part, it will be necessary for those interested in presenting papers to this Section to submit the title, and a short abstract, to the secretary several weeks earlier than the usual time. Every one interested in the work of this Section is invited to take part and asked to forward all titles and abstracts to the secretary as promptly as possible.—HENRY M. BURLAGE, *Chairman.* L. W. RICHARDS, *Secretary,* School of Pharmacy, University of Montana, Missoula, Montana.

While the foregoing has been inserted by the officers of the Section on Practical Pharmacy and Dispensing, it applies to all Sections and Conferences. For officers—see the roster in this issue of the JOURNAL.

PHARMACEUTICAL SERVICE IN THE ARMY.

Representatives of the AMERICAN PHARMACEUTICAL ASSOCIATION, The American Association of Colleges of Pharmacy and the National Association Boards of Pharmacy met in Washington on April 5th and 6th, to continue the joint efforts to improve the pharmaceutical service for the Army and to secure better recognition for pharmacists by improving their status.

Plans to broaden the work of army pharmacists were considered. Visits at the invitation of the Surgeon General were made to the hospitals at the Medical Center and at Fort Myer. The pharmacies at those hospitals and the work carried on in them were carefully inspected. A conference with Surgeon General Patterson and Colonel McDonald was held during which proposed legislation looking to a commissioned rank for army pharmacists was discussed.

It is expected that a similar joint committee meeting will be held in Washington during June or July and that an encouraging report of progress can be made at the Portland, Oregon meeting, August 5th–10th. The efforts to secure a satisfactory status for pharmacy in the Army and the Navy have been interrupted by the reductions affecting these services during the depression. This work is being taken up aggressively again and when a satisfactory program is worked out the national, state and local associations will be informed and their coöperation requested.

EDITORIAL NOTES

KENTUCKY FARM FOR NARCOTIC ADDICTS.

The $4,000,000.00 narcotic farm established by the Federal Government in the heart of Kentucky's blue grass country for the segregation and rehabilitation of narcotic addicts will be dedicated May 25th, by Surgeon General Hugh S. Cumming.

Construction of the huge plant, which covers eleven acres in the centre of a 1000-acre farm tract acquired by the government, began in the Spring of 1932. A similar institution is being erected at Fort Worth, Texas.

Efforts will be made to restore to health and train to be self-supporting and self-reliant those who are admitted. Experiments will be carried on to determine the best methods of treatment.

The farm staff will number several hundred with an annual payroll of slightly less than $500,000.00. Additional operating costs will bring the yearly cost to about $750,000.00.

A REPORTED POISONING CASE.

A case of poisoning in Brooklyn reported in the press, is now before the Grand Jury, hence names are not mentioned. References to a married man whose wife and three children died between the last of March and middle of April. The Police Department in Brooklyn, struck by the coincidence, had post-mortem examinations made and thallium was found in the viscera. Chemical analysis by spectroscope revealed the presence of thallium, not only in the viscera but in some cocoa. However, ordinary chemical analysis failed to detect thallium.

Mention is made because of the article in this issue by James C. Munch.

CHIEF OF THE BUREAU OF MEDICINE AND SURGERY.

By an act of Congress, March 3, 1871, it was provided that "the chiefs of the bureaus of medicine and surgery, provisions and clothing, steam engineering and construction and repair, shall have the relative rank of commodore, while holding said position, and shall have, respectively, the title of surgeon general, paymaster general, engineer in chief and chief constructor." The first to bear this new title of Surgeon General, though the fifth to hold office as Chief of the Bureau of Medicine and Surgery, was William Maxwell Wood of Maryland.

PHARMACEUTICAL MUSEUM FOR MOSCOW.

The *Pharmaceutical Journal* of April 27, 1935 states that "a pharmaceutical museum has been opened in Moscow. The first dispensary in Russia was founded by the English pharmacist, Jameson French, in 1651, but it was intended exclusively for the service of the Tsar, his family and members of the Court. In 1675 a second crown pharmacy was opened in Moscow, and this was empowered to supply medicines to the public. The following year, in 1701, Peter I ordered the opening of eight chemists' shops in Moscow. At the present time Moscow possesses ninety-eight chemists' stores, but over 50 per cent of the prescriptions are dispensed by Moscow's three pharmaceutical factories. In 1923 817,000 prescriptions were dispensed in Moscow, in 1933 they made up 4,700,000."

VITAMIN "A" AND "D" PRODUCTS.

The Food and Drug Administration has received numerous inquiries about the proper labeling of products represented to contain vitamins A or D or both.

Many products compare their vitamin A and D potency with a stated volume of cod liver oil. If statements of this character are made, they should be literally true. For example, if the label of a medicine states "Each tablet equals one teaspoonful of cod liver oil in vitamins A and D potency," it should contain the same number of vitamin A and D units as would be contained in not less than 4 cc. (3.67 Gm.) of cod liver oil, of U. S. P. potency. In terms of the U. S. P. standard for cod liver oil which became official on January 1, 1935, this would require each tablet to contain not less than 2200 units of vitamin A and not less than 312 units of vitamin D.

Manufacturers should state vitamin A and D potencies in terms of the new U. S. P. units. Because differences in the clinical efficacy of vitamin D from different sources have been reported, it is desirable, and in many instances necessary in order to meet the requirements of the Federal Food and Drugs Act, to state the source of the vitamins A and D. For example, "From cod liver oil." All direct and implied claims comparing products of this sort with cod liver oil should be true in terms of the new standard for cod liver oil.—W. G. CAMPBELL, *Chief*.

PERSONAL AND NEWS ITEMS.

The *Southeastern Drug Journal* devoted a number of pages of its May issue in honoring Dr. James H. Beal.

The frontispiece of these pages is a half-tone of the honored member. Among the tributes the first is that of the Florida Pharmaceutical Association presented by its president, Don S. Evans; the State Board of Pharmacy, by W. M. Hankins; the University of Florida, by Dean Townes R. Leigh; The Traveling Mens Auxiliary, by its president, Rush St. John; the officers of the State Association, by Max S. Adler, Secretary G. H. Grommet, Victor Wray, C. G. Hamilton, W. E. Fossett, E. P. Purcell, Wm. R. Emrich, John K. Clemmer, J. K. Atwood; and the wholesale industry of Florida, by H. C. Shuptrine and F. C. Groover.

A testimonial dinner was tendered **Dean Ernest Little** on May 20th, honoring him for his services to Pharmacy. Recognition was given to the various services rendered by the Dean and notably this year, fulfilling the office of president of the American Association of Colleges of Pharmacy. The dinner was well attended and a delightful and interesting program carried out under the direction of a committee of members of the A. PH. A. Branch, Rutgers University, local and state organizations and other friends.

Former President, A. PH. A., **Robert L. Swain,** Deputy Food and Drug Commissioner for Maryland, has been reappointed to the Maryland Board of Pharmacy. At the commencement exercises of Washington College, Chestertown, Md., the degree of doctor of laws will be conferred on him, and also on Dr. John H. Rowland, dean of the Medical School of the University of Maryland.

Col. Charles Ransom, Medical Corps, succeeds Major General Robert U. Patterson as Surgeon General, the term of the former expiring May 31, 1935.

Z. C. Lewis, Montgomery, has been appointed secretary of Alabama Pharmaceutical Association.

Paul C. Olsen recently made a factual study of the results of stabilization in a typical city retail drug store. A second of a series of investigations to determine from actual facts just what profits drug store proprietors are really obtaining on products on which price stabilization policies have been announced and on those not announced is being studied and reports may be obtained from Secretary E. L. Newcomb, N. W. D. A.

The Library Facilities of Washington lists the library of the AMERICAN PHARMACEUTICAL ASSOCIATION.

Boericke & Tafel, homeopathic pharmacists, of Philadelphia and New York are celebrating the conclusion of the first century of this establishment which later added other branches.

The *Scientific Bulletin*, published by Laboratorio Quimico Central, City of Mexico, of April 15th, carries a news item, advising that Secretary A. L. I. Winne, Virginia Board of Pharmacy, visited in the City of Mexico. The *Bulletin* thanked E. G. Eberle for advising the staff of Mr. Winne's visit and welcomes members of the AMERICAN PHARMACEUTICAL ASSOCIATION. Director G. G. Colin has been a member of the ASSOCIATION for a number of years and is chairman of the Membership Committee for Mexico.

A distinctive professional window display has been designed by Merck & Co., Inc., for distribution to retail pharmacists who desire to feature their prescription service to the public. This attractive five-piece lithographed presentation is intended to portray the professional alliance of the physician, the pharmacist and the manufacturing chemist in promoting health and combating disease.

The Mississippian of recent date featured the School of Pharmacy of which **Prof. E. L. Hammond** is dean.

In a booklet of "Architects and Sculptors of the Principal Buildings and Monuments in Washington, that of the AMERICAN PHARMACEUTICAL ASSOCIATION is listed and John Russell Pope as the architect. The latter is also credited with the Archives Building, Theodore Roosevelt Memorial, Strauss Memorial, Constitution Hall and Scottish Rite Cathedral.

Secretary E. F. Kelly was a speaker at the Illinois Pharmaceutical Association held at Quincy during the week of May 21st, his subject being—"The Value and Defects of the Retail Drug Code;" **Samuel C. Henry** spoke on "Problems Facing the Drug Trade." **W. Bruce Phillip** was a guest at the Chicago Veteran Druggists' Association.

John C. Emerson, Joplin, is the new president of Missouri Pharmaceutical Association, and **Kenneth Nichols,** of Jefferson City, is the new secretary.

The *Pharmaceutical Journal*, Great Britain, expressed its loyalty and congratulations to King George in the "Silver Anniversary" edition of May 4th.

Among recent visitors at the American Institute of Pharmacy are the following: Ernest L. Cushing, Charlestown, Mass.; Samuel A. Weiss, New York City; Dr. Arthur E. Kennelly, Harvard University; Dr. C. M. Judd, Rochester, Minn.; Charles E. Lyman, New London, Conn.; Ralph P. White, Youngstown, Ohio; Dean R. A. Lyman, Lincoln, Neb.; Dean Ernest Little, Newark, N. J.; G. T. MacDonald, Shelburne, Nova Scotia; Sam E. Welfare, Winston-Salem, N. C.; A. J. Du Plessis, Middleburg C.P., South Africa; Dorothy Clapp, St. Paul, Minn.; Mr. and Mrs. T. J. McAuliffe, Swampscott, Mass.; C. A. Northrup, Visalia, Calif.; Robert L. Swain, Jr., Washington College, Maryland; Paul A. McNeil, librarian of Oliveira Lima, Catholic University of America; W. M. White, U. S. Public Health Service; Joseph A. Hailer, United Drug Co., Boston; Esther H. Barney, Chicago, who so efficiently supervised the AMERICAN PHARMACEUTICAL ASSOCIATION Exhibit at the World's Fair, Chicago.

OBITUARY.

LAWRENCE S. WILLIAMS.

Lawrence Soper Williams, member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1910, died April 25th, aged 48 years, after an illness of six weeks.

Mr. Williams was a pharmacist in devotion and action, who had pride in his profession and

L. S. WILLIAMS.

gave patrons and physicians a better appreciation of pharmaceutical service, and is expressed in his address before the Section on Practical Pharmacy in Washington and published in this number of the JOURNAL. His loyalty and enthusiasm were emphasized in an address at the Washington meeting when he was representative of his classmates, and in the presentation made of a wonderful collection of show globes and other museum material. (See June JOURNAL, 1934, page 608, and in September issue, page 947.) These words speak in part for the pharmacist, who was always ready to espouse the cause of pharmacy and had pride in his profession, evidenced by precept and example.

Mr. Williams served as president of the Maryland Pharmaceutical Association in 1930 after having been third, second and first vice-president in successive years. After his term as president he was a member of the executive committee. For more than twenty years he had conducted his pharmacy at Caroline and Preston Streets, Baltimore. He started his collection of show globes many years ago and added to these balances, mortars and other collections, and a large selection of these are on permanent display at the American Institute of Pharmacy and expressive of his devotion—a gift to the ASSOCIATION.

The deceased was born in Baltimore, attended the public schools here, studied at Baltimore City College and the University of Maryland School of Pharmacy.

Surviving are his widow, the former Ida Exall, and three children, Marguerite, wife of Dr. Albert E. Sikorsky, and Sarah Williams and Lawrence S. Williams, Jr.

Mr. Williams was a member of the Masonic Order, the Old Town Merchants and Manufacturers' Association and the Baltimore Retail Druggists' Association, in which he had been an officer.

ROBERT R. LAMPA.

Robert R. Lampa, member of the AMERICAN PHARMACEUTICAL ASSOCIATION since 1892, died at his home in Teaneck, N. J., April 29th, aged 72 years.

Born in Germany, Mr. Lampa came to this country with his parents, and at the age of fifteen obtained a position as errand boy for Lehn & Fink. He studied at night at Cooper Union and later at Columbia University, graduating from both institutions. He went successively into the botanical, drug and chemical departments of the firm, and then was taken into the office as city salesman. After a few years he was made New England representative and served in this post until he was elected vice-president. He retired several years ago to devote his time to his pet hobbies of literature and the sciences generally. He published a book of poems called "Stardust," and for many years was poet laureate for the New York Veteran Druggists' Association of which he had been president twice.

JOHN P. SCHOENTHALER.

We are just advised of the death of our fellow-member, John P. Schoenthaler, of St. Louis, on February 19th, aged 73 years. The deceased affiliated with the AMERICAN PHARMACEUTICAL ASSOCIATION in 1901.

HON. CLYDE KELLY.

The unfortunate death of Hon. Clyde Kelly of Pennsylvania, on April 29th, is a severe blow to all those who hope for Federal legislation to prevent unfair trading. Congressman Kelly believed implicitly in the benefits to be derived from the legislation known as the Capper-Kelly Fair Trade Bill. He thoroughly understood the principles of this legislation and argued eloquently and worked hard in its behalf. The Capper-Kelly Bill, of which he was co-author with Senator Arthur Capper of Kansas, came near to carrying out the realization of his boyhood ambition and aim.

It was due to Congressman Kelly's leadership and sagacity that the NIRA was so framed that limited price stabilization was possible. To the independent retailer his devotion to fair trading endeared him to their hearts. That which can be done best to perpetuate his memory is for every independent retailer and for all drug organizations to fight on aggressively and have Congress pass the legislation that he fathered.—From *W. Bruce Phillips Bulletin*, April 30, 1935.

DEATH OF DR. WILHELM KOLLE.

Dr. Wilhelm Kolle, privy councilor and director of the State Institute for Experimental Therapy and of the Chemicotherapy Research Institute, George Speyer Haus, at Frankfort, died in Wiesbaden, May 10th, after a long illness at the age of 66.

In 1893 Dr. Kolle entered service of the Robert Koch Institute for infectious diseases in Berlin. By order of the State Government, he directed a scientific expedition in South Africa from 1897 to 1899, studying the treatment of leprosy and rinderpest. He was sent on a similar mission to the Sudan by the Egyptian Government in 1900.

He was appointed professor of Bacteriology at Bern University in 1906. He succeeded Paul Ehrlich as director of the Frankfort Institute in 1915. For a long time he was a member of the permanent standardization commission for therapeutical and bacteriological medicine of the League of Nations' hygiene committee.

At his death Dr. Kolle was working on elaborate scientific plans particularly connected with cancer research.

CANADIAN HEALTH INSURANCE.

According to the *Canadian Pharmaceutical Journal*—on the Commission which Canada proposes to set up there must be a place for the pharmacist, who is one of the health factors in the community. In England under a National Health Insurance he has a definite and responsible position and is recognized in the scheme of things. In the various provinces are established Schools of Pharmacy to educate young men to have a knowledge of drugs and medicines and their compounding. The service the pharmacist renders the community in case of sickness is immeasurable. The diploma hanging on his wall is a guarantee of competency in compounding drugs, and we feel sure that the Hon. Dr. Sutherland will include the pharmacist among his appointees to the Royal Commission which he proposes to set up to inquire into State Medicine and Health Insurance.

The *American Professional Pharmacist* has succeeded the *Practical Druggist*, the Editorial Board is composed of Reginald E. Dyer, A. O. Mickelsen, John L. Dandreau and C. Leonard O'Connell.

Make arrangements early to attend the Portland A. PH. A., meeting.

SOCIETIES AND COLLEGES.

AMERICAN COUNCIL ON EDUCATION.

The 18th annual meeting of the American Council on Education was held in Washington, May 3–4, 1935. As members of the Council, the American Association of Colleges of Pharmacy was represented by Dean Ernest Little of Rutgers and Dean Rufus A. Lyman of Nebraska. Among the speakers of the meeting, known to pharmacy, Dr. W. W. Charters delivered an interesting address on "The Motion Picture in Education." The long list of addresses and papers dealt with educational subjects in various phases. Director-Emeritus Dr. Charles Riborg Mann was honored at a dinner presided over by Dr. Frederick B. Robinson of the College of the City of New York.

The American Council on Education was founded in 1918 by prominent educators representing a majority of the national educational associations.

BALTIMORE AND D. C. VETERANS' ASSOCIATIONS.

The annual joint outing of the fraters of the Veterans' Associations of Baltimore and the District of Columbia was held at Olney Inn, May 8th. A beautiful day induced a large attendance. Ladies graced the occasion.

NATIONAL CONFERENCE OF PHARMACEUTICAL RESEARCH.

Chairman E. N. Gathercoal has addressed the members on the meeting of the National Conference on Pharmaceutical Research at Portland, August 3rd. The annual survey and proceedings of last year were referred to in the February JOURNAL on page 177. Chairman Gathercoal hopes for a large attendance and an interesting program.

He refers to the pharmaceutical tour from Chicago to Portland and return, references to which are made in the April JOURNAL and also in this issue.

CENSUS OF RESEARCH, 1934–1935.

Dr. James C. Munch, 40 North Maple Ave., Lansdowne, Pa., desires prompt information relative to research being conducted in laboratories and by individuals. In making the report to him the name of the reporter should be given, the laboratory address, the field of investigations and the subject or subjects under investigation. Prompt replies are requested.

GEORGE WASHINGTON UNIVERSITY FELLOWSHIPS.

The School of Medicine of George Washington University announces the acceptance of several grants for various research projects as follows: From the Rockefeller Foundation the sum of $25,500.00 in support of studies in the department of biochemistry; a renewal of the Kane-Kotz Fund of $1700.00 for studies on clinical endocrinology in the department of obstetrics and gynecology; from the Eli Lilly Co. the sum of $1200.00 for a fellowship in biochemistry, and a grant of $1800.00 for the study of the post-pituitary hormones from Parke, Davis and Company.

AMERICAN PHARMACEUTICAL MANUFACTURERS' ASSOCIATION.

The American Pharmaceutical Manufacturers' Association will meet at Hershey, Pa., June 3rd–6th, in the foothills of the Blue Ridge Mountains overlooking Lebanon Valley.

AMERICAN DRUG MANUFACTURERS' ASSOCIATION.

The Wagner bill was a subject of considerable discussion and opposition at the annual meeting of the American Drug Manufacturers' Association at Hot Springs, May 6th to 9th. The executive committee was of the opinion that the Copeland bill required amendment. Tariff bargaining received much attention, the director of Foreign and Domestic Commerce addressed the convention on this subject.

The reports of the officers and of the standing committees conveyed timely and useful information on matters relating to the drug industry and the members of the association in particular.

The annual election resulted in naming the following officers for the ensuing year:

President, A. C. Boylston, St. Louis; *First Vice-President*, Oscar W. Smith, Detroit; *Second Vice-President*, John F. Anderson, New Brunswick, N. J.; *Third Vice-President*, L. N. Upjohn, Kalamazoo, Mich.; *Executive Vice-President and Secretary*, reëlected by the executive committee, Carson P. Frailey, 506 Albee Building, Washington; *Treasurer*, S. DeWitt Clough, North Chicago, Ill.; *General Counsel*, Horace W. Bigelow, Detroit.

MARYLAND AND DISTRICT OF COLUMBIA ASSOCIATION.

The Maryland and District of Columbia Pharmaceutical Associations will meet in Baltimore, June 25th–28th.

WEST VIRGINIA UNIVERSITY.

Students of West Virginia University, Department of Pharmacy, toured May 5th in a caravan of six cars to visit the plant of Parke, Davis & Co., in Detroit. The group was accompanied by Prof. and Mrs. J. Lester Hayman.

MINNESOTA ASSOCIATION.

The following results of the recent mail ballot of Minnesota Pharmaceutical Association have been announced: *President*, Roy G. Paulson, Fairmont; *Vice-Presidents*, Jesse B. Slocumb, St. Paul; Orlando Didra, Waseca; and L. M. Herbert, Worthington; *Secretary*, A. Roy F. Johnson; *Treasurer*, Charles T. Heller, Jr., St. Paul; *Executive Committeeman*, Joseph Vadheim, Tyler.

KANSAS ASSOCIATION OFFICERS.

Kansas Pharmaceutical Association met in Wichita, April 9th to 11th; the following officers were elected: *President*, A. H. King, Manhattan, a member of the State Board of Pharmacy for nine years; *First Vice-President*, Percy S. Walker; *Second Vice-President*, Paul Schultz, Beloit; *Treasurer*, Walter Varnum, and Dean Havenhill, Lawrence, was renamed librarian.

It is contemplated to urge the use of the funds of the State Board of Pharmacy to underwrite the publication of the "History of Pharmacy in Kansas," by Matt Noll.

GOLDEN ANNIVERSARY MEETINGS.

The Chicago Retail Druggists Association has held its 50th anniversary meeting. A most interesting program was provided and carried out and a special edition of the *C. R. D. A. News*, May 4th, was issued. The celebration took place at College Inn, Hotel Sherman, and was participated in by the members and representatives of national, state and local organizations. The Jubilee banquet was held on May 9th.

Tennessee Pharmaceutical Association will celebrate its 50th anniversary July 15th–18th in Memphis. Elaborate preparations are made for the event under direction of Chairman Ed. Sheely.

U. S. P. AND N. F. PUBLICITY COMMITTEE, MARYLAND.

The sixth group of prescriptions has been mailed to Maryland physicians under the direction of Chairman Marvin J. Andrews. These comprise preparations for Dermatitis, Anti-Pruritic Lotion, Insect Skin Lotion, Poison Ivy, Acne, Prickly Heat Lotion, Burns, etc. Criticisms and suggestions are invited and the work has been eminently successful.

IMPROVED METHOD CUTS COST OF MAKING CALCIUM GLUCONATE.

A cheaper and faster method for making calcium gluconate, commonly prescribed for expectant mothers and others who need calcium, was reported April 23rd, before the American Chemical Society in New York City by H. T. Herrick, R. Hellbach and O. E. May, chemists of the U. S. Department of Agriculture.

The discovery is based upon a more efficient use of molds as fermentation agents. Molds have been used for centuries in the manufacture of Roquefort and Camenbert cheese, and more recently for making citric and gluconic acid.

Six years ago Herrick and May discovered a mold that produces gluconic acid from glucose or corn sugar. This acid is important in the manufacture of calcium gluconate, which until that time sold for about $150.00 a pound. When this pure-culture mold was put to work making gluconic acid the rare chemical could be made for 50 cents a pound. The improved process now cuts the cost still more.

Because molds must have air—the same as most other forms of plant life—the chemists grew them on the surface of shallow pans in the laboratories of the Bureau of Chemistry and Soils, at Arlington Farm, Va. The method can be adapted to commercial use but the necessity of using large pans has been a decided handicap in large-scale operations.—Information from the U. S. Department of Agriculture.

Dr. Howard B. Lewis, director of the College of Pharmacy of the University of Michigan and professor of physiological chemistry in the Medical School, has been elected a member of the National Board of Medical Examiners of the United States, to succeed the late Professor Otto Folin, of Harvard University.

LEGAL AND LEGISLATIVE.

CODE MEETING.

A meeting of delegates representing various codes was held in Washington, Constitution Hall, May 22nd. The urgency of continuation of the NRA for a period of two more years was voiced and the progress made under present conditions, even though largely initiative, was generally voiced.

Steps were taken to impress the continuation on Congress.

STATE LEGISLATURES.

The following legislatures are still in session: Alabama, California, Connecticut, Florida, Illinois, Massachusetts, Michigan, Missouri, Nebraska, New Hampshire, New Jersey, North Carolina, Ohio, Pennsylvania, South Carolina, Texas, Wisconsin; other states had no sessions or have adjourned.

FOOD AND DRUG BILL.

An agreement is said to have been reached by Senators Royal S. Copeland and Josiah W. Bailey. The principal matters involved in the agreement include:

1. A separate definition for devices, removing them from classification as drugs.
2. A definition of scientific opinion.
3. A variations clause similar to that in the present law.
4. False advertising to be classed as misbranding instead of adulteration.
5. Liberalization of the definition of "germicide."
6. A more restricted provision for factory inspection.
7. Multiple seizures prohibited in charges of misbranding except where imminently dangerous to health, and provision for consolidating multiple seizures for a single trial.
8. Specific provision that no power is taken from the Federal Trade Commission.

NATIONAL RECOVERY ADMINISTRATION.

At a conference, on May 16th, with the National Industrial Recovery Board the President approved the following recommendations which had been unanimously adopted by the Board and submitted to him.

1.—Two-year extension. This time is necessary to obtain the coöperation of industry in the formulation of codes, with assurances to management and labor of reasonably permanent conditions. It is necessary code administration; to strengthen enforcement through judicial approval of methods; and to prevent the entire breakdown of labor and fair trade practice provisions by chiselers who are already at work undermining the standards of fair competition. The extension of NRA for a few months will bring rapid deterioration and disintegration of the whole industrial recovery program.

2.—Adequate period for the revision of codes—three to six months.

3.—Improved statement of legislative policies and standards to give additional guidance and authority for administrative action.

4.—Jurisdiction of NRA limited to industries engaged in, or SUBSTANTIALLY affecting interstate commerce. This will prevent the NRA from taking in too much territory and will strengthen its legal authority.

5.—Provision for voluntary codes and adequate authority for imposition of *limited codes. Both* are necessary. Voluntary codes to encourage improved business practices, including appropriate labor provisions. Limited codes to insure minimum wages, maximum hours, prohibition of child labor and Section 7(*a*).

6.—Definite authority and standards for the NRA *to prevent unfair competitive practices,* especially those tending to monopoly and destruction of small enterprises.

7.—Methods of code making and enforcement should be further defined; with enforcement primarily through injunction or cease and desist orders, and with provision for adequate protection of individual rights and small enterprises through opportunity for hearing and judicial review, and public control of all compulsory processes.

MARYLAND LEGISLATION.

The *Maryland Pharmacist* defines and explains new Maryland legislation: The Gross Receipts Tax—the accounts received are for purposes of unemployment relief and old age pensions. Drug Store Permit Law.—Under this law, no person, copartnership, association or corporation may operate, maintain, open or establish any pharmacy in this state except under a permit issued by the Maryland Board of Pharmacy.

Permits are required for the manufacture of drugs, medicines, etc.

All false and misleading therapeutic claims are barred from the label of all drugs and medicines.

Poison Law.—This law repeals the Old Poison Law, enumerates the poisons, defines labels; the law deals only with sales at retail. Drug Store Inspection Law.—Under this law every drug store must possess the later revisions of the U. S. Pharmacopœia and National Formulary and must be properly equipped.

The Maryland Board of Pharmacy and the State Department of Health are given power to inspect all drugs and medicines manufactured or sold within the state, and to inspect during business hours any pharmacy or other place where drugs or medicines are manufactured or kept for sale.

Barbital Law.—This law prohibits the sale of barbital, trional, etc., except on prescriptions. Pure Food and Drugs Act adds labeling and misrepresentation clauses. Patent Medicine shows and unsafe sampling are prohibited under House Bill 604.

The State Narcotic Law repeals the old State Narcotic Act and replaces it with an improved version of the Uniform State Narcotic Act. The records under the Federal Narcotic Act are expressly adopted under the State Act.

The foregoing are very brief statements abstracted from the report referred to.

RESTRICTIONS ON SALES IN OHIO.

Acting within its authority to issue regulations and extend the list of drugs confined to sales by registered pharmacists, the Ohio State Board of Pharmacy has made material additions to its list of drugs which cannot be sold through general merchants. The list comprises more than 200 items.

Columbus, Ohio.—The Ohio State Pharmaceutical Association and the Ohio Board of Pharmacy are objecting to a provision in the bill which permits doctors to dispense a maximum of four grains of opium or its equivalent in other narcotics without prescription.

JAPANESE SCHOOLS OF PHARMACY.

Dr. Yoshio Sugii, dean of the Women's Department in the Tokyo College of Pharmacy, was appointed the head-pharmacist of the hospital attached to the Hokkaido Imperial University, and his former post is now occupied by Professor Shichiro Akiya, of the same college. The Tokyo College of Pharmacy is situated at Ueno Sakuragi-cho, Shitaya-ku, Tokyo.

The American Association of Colleges of Pharmacy was accepted as an associated society of the American Association for the Advancement of Science.

CONGRESS OF PHARMACY.

The Congress of Pharmacy, as before stated, convenes in Brussels, July 30th to August 6th.

A program of the papers which are to be submitted to the Scientific Section of the International Congress of Pharmacy has been published in the *Journal de Pharmacie de Belgique*. Among the papers to be presented are the following:

Prof. J. H. Burn, on "The Standardization of Oestrin and Male Hormone;" H. Berry on "The Stability of Strophanthin Solution;" T. E. Wallis on "Structural Standards for Crude Drugs;" Dr. W. H. Linnell on "Halogen Analogues of Ephedrine and Adrenaline;" A. La Grange and N. Wattiez, "A Critical Study of the Methods of Assay of the Alkaloids in the Official Preparations of Belladonna in the Belgian Pharmacopœia, 1930;" A. J. J. Van der Velde, "Research on the Sterilization and Biochemical Control of Pharmaceutical Products;" Prof. Herrmann and Monsieur Hebert, "Criticisms on the Socalled Chemical Reactions of Cannabis Indica;" Monsieur Snejko's "The Problem of Unifying Pharmaceutical Nomenclature in an International Pharmacopœia."

On Saturday and Sunday, August 3rd and 4th, the Congress goes to Antwerp to celebrate the centenary of the Societe de Pharmacie d'Anvers, and closes officially on August 5th.

FAIR TRADE LEGISLATION.

California, Iowa, Maryland, New Jersey, New York, Oregon, Washington, Wisconsin enacted a Fair Trade law. Alabama, Connecticut, Indiana, Michigan, Minnesota, Montana, Nebraska, Nevada, Oklahoma, Pennsylvania, South Dakota, Texas, Utah, Wyoming introduced fair trade bills.

George A. Bunting entertained members of the Baltimore Veteran Druggists' Association at his home, for those whose birthdays were celebrated in April; among them, the host, Frank C. Purdum, A. G. DuMez and William G. Lauer.

Make arrangements early to attend the Portland A. Ph. A., meeting.

THE PORTLAND MEETING OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

The following paragraphs are culled from the letters of President R. P. Fischelis and Local Secretary A. O. Mickelsen:

"In less than three months the AMERICAN PHARMACEUTICAL ASSOCIATION will hold its Eighty-Third annual meeting at Portland, Oregon. For the first time in its history the ASSOCIATION has selected the Pacific Northwest as its center of activities for the week which is annually devoted to planning the major activities of American Pharmacy for the ensuing year. Much has occurred since we met in Washington, D. C., to dedicate the Headquarters Building, and the officers and committees will have reports to present at the annual convention which will be full of important and valuable information both from a scientific and a practical standpoint."

"The State Pharmaceutical Associations of Oregon, Washington and Idaho will hold a history-making tri-state convention in Portland, August 4th to 6th, which will add greatly to the interest and attendance of the A. PH. A. convention.

"The Bonneville Dam, a $32,000,000.00 project, will be visited by A. PH. A. delegates on Saturday, August 10th, when they will be taken up the world-famed Columbia River Highway for an all-day scenic drive and luncheon featuring famous Columbia River salmon. No other section in the world could duplicate this pleasure trip."

DETROIT BRANCH, A. PH. A.

The College of Pharmacy, University of Michigan and the Detroit Branch of the AMERICAN PHARMACEUTICAL ASSOCIATION sponsored a meeting for May 23rd. President Alexander G. Ruthven, of the University, welcomed the visitors and members. Dean Charles B. Jordan discussed Food, Drug and Cosmetic Legislation; Edgar H. Gault spoke on "The Ethics of Modern Advertising," Dr. Louis H. Newburgh's subject was "Drugs and Nutrition," and Dr. H. H. Willard presented "Ultra-Violet Fluorescence as Applied to Problems of Chemistry and Pharmacy." A dinner was part of the program and the Branch elected officers for the ensuing year.

GOLDEN JUBILEE MEETING OF THE NATIONAL EDITORIAL ASSOCIATION.

Celebrating the 50th birthday of the National Editorial Association, prominent personages of the Fourth Estate gathered at New Orleans, May 4th–12th, from all parts of the nation to participate in an outstanding program for its 50th Anniversary meeting.

RETAIL DRUG TRADE BUDGETS.

The National Code Authority for the Retail Drug Trade has made application for extension of its Budget and Basis of Contribution and of the Budgets and Bases of Contribution for certain of its Local Committees which were approved for the period from November 1, 1934, to April 30, 1935, such extension to cover the period from April 30, 1935, to June 16, 1935. The National Industrial Recovery Board has May 13th signed an Order, No. 60–430, approving such extension, such approval being effective fifteen (15) days from the date hereof unless prior to that time good cause to the contrary is shown and a subsequent order is issued.

In a letter directed to *all* Code Authorities, released May 15th, the National Industrial Recovery Board sharply differentiated between code administration and trade association activities, advising code authorities that expenses for trade association functions would not be approved unless such activities are specifically authorized in the code.

THE NRA DECISIONS.

The general views expressed in the press that the NRA would be granted extension were typed for these columns, but had to be deleted as the decisions of the United States Supreme Court, of May 27th, necessitate action, by Congress. The general opinion in Administration circles now is that the NRA can be redrafted to conform with the decisions; under the conditions that have developed there is no certainty as to what the effect of the decisions will mean in connection with pending legislation.

The decisions should stimulate study and coöperative action by code authorities, the divisions of the industry and the organizations which are in accord relative to the possibilities of establishing fair trade practices as contemplated by the codes.

The Texas Legislature amended the Texas Pharmacy Law lowering the annual renewal certificate fee from $3.00 to $2.00 and the members of the Board of Pharmacy are allowed $10.00 per day during active work at examination sessions.

BOOK NOTICES AND REVIEWS.

A Text Book of Pharmacognosy. By GEORGE EDWARD TREASE, B.Pharm., PhC., Lecturer on Pharmacognosy in the University College of Nottingham, with contributions by H. H. Barker, W. R. Heading, H. M. Hirst and A. H. Ware. vi + 653 pp., 187 figs. Baltimore, Wm. Wood and Co., 1935. Price $6.00.

This new text in pharmacognosy is stated by its English author to cover the requirements in pharmacognosy of students reading for pharmaceutical examinations in most English-speaking countries.

Its contents are arranged in three parts, an appendix and index. Part I, entitled "General Principles," comprising 132 pages, contains a brief chapter on historical pharmacognosy which is followed by a chapter dealing with the cultivation of medicinal plants by H. M. Hirst, and by three chapters dealing, respectively, with enzymes, vitamins and hormones by H. H. Barker. There next follow chapters by the author on the collection, drying and storage of drugs, insects and other pests in drugs, London commerce in crude drugs, one on plant principles and their extraction by W. R. Heading, another on tests for plant phenols as an aid to drug identification by A. H. Ware and two by the author on the microscope as an aid to drug identification and filtered ultra-violet light as an aid to drug identification.

Part II, entitled "Drugs of Vegetable Origin," comprising 462 pages, contains a chapter called "Introduction" which briefly summarizes some facts concerning plant classification and nomenclature, and eight chapters dealing with the drugs of the Thallophytes, Pteridophytes, Gymnosperms and Angiosperms which the author has arranged into phyla and subphyla.

Part III contains an introductory chapter of a page dealing with classification of animal drugs and a chapter on animals and animal products. The appendix contains nearly six pages devoted to a glossary of Latin words used in naming species.

In adopting the taxonomic method of presenting the subject matter on animal and vegetable drugs the author has followed what the experience of many of his fellow teachers have found to be more satisfactory than the morphologic method. A condensed morphological classification in addition, however, would seem desirable especially for correlating the drugs representing similar organs or cell contents.

The chapter on the cultivation of medicinal plants is well written and gives sufficient information on this topic for the time allotted for their presentation of this phase of pharmaceutical botany in the average undergraduate curriculum. For purposes of the growers of medicinal plants, however, the information given under many of the species is too scant to be regarded of more than elementary value.

The chapter on hormones is on the whole well written and an innovation in the average pharmacognosy text. It is somewhat surprising that we note no mention under the Anterior Pituitary of the hormones Prolan-A and Prolan-B, and no mention of the hormone Progestin of the Corpus Luteum.

Another innovation in a text of this kind is the chapter on "Filtered Ultra-Violet Light as an Aid to Drug Identification." Fluorescence analysis as applied to crude drug identification has made rapid progress within the past decade and its evidence is often of some value in pharmacognosy when taken in conjunction with evidence derived from other sources. The fundamentals of this comparatively new field including an adequate description of the Hanovia analytic quartz lamp and brief notes on the examination of types of pharmaceutical products are included in this chapter.

In the consideration of most of the crude drugs, the following order of treatment is noted: British pharmacopœial title or general Latin title, synonyms, source and collection, history, characters, constituents, substitutes and uses. Under characters, the physical characteristics are given with usually the outstanding diagnostic histological features.

It is surprising that one finds no mention of powdered drugs in various drug monographs, especially since this phase of pharmacognosy is usually more needed in general pharmaceutical work than that of identifying the whole drug. In many instances, also, the treatment of the microscopical characteristics of the whole drug is inadequate, and insufficient data are given on adulterants. Most of the figures are good and have been borrowed from a variety of sources.

The work as a whole is creditable and should serve as a text on pharmacognosy in colleges where British standards are taught providing

the data on histological details and adulterants and substitutes are amplified in the lectures. It may well serve as a reference for students of pharmacognosy generally.—H. W. YOUNGKEN.

Annual Survey of American Chemistry. Volume IX, 1934, edited by CLARENCE J. WEST, Director, Research Information Service, National Research Council, published for the National Research Council, by Reinhold Publishing Corporation, New York; 400 pages. Price $4.50.

The Annual Survey of American Chemistry for 1934 follows the same general principles as preceding volumes with the exception that this year the chapter on Biochemistry has been omitted. The reason assigned for the omission is that the Annual Survey of Biochemistry is fully covered by the Annual Survey of Biochemistry published by the Stanford University Press. Most of the contributors have been represented in previous volumes, all of them outstanding in their special fields. The volume has 400 pages and is presented in twenty-five chapters, half of them are concerned with industrial subjects and suggest the trends in the industry as well as the accomplishments of the period.

Each chapter is followed by references, citing the subjects discussed. The Authors' Index, in three columns, covers twenty pages and gives an idea of the completeness with which the subjects are dealt.

Previous volumes have been reviewed in this publication and the favorable comments made in these editions apply to this volume.

The Law of Patents for Chemists. By JOSEPH ROSSMAN, Patent Examiner, U. S. Patent Office, member of the bar of the U. S. Court of Customs and Patent Appeals and the U. S. Supreme Court, editor of the *Journal of the Patent Office Society*, published by the Williams and Wilkins Co., Baltimore, Md. Price $4.50.

The publishers state that this is a work both for study to familiarize the reader with the essentials of Patent Law and for regular reference and to guide the inventor in practical matters pertaining to his protection. These matters are discussed in Part I. Part II discusses the essentials of Patent Law principles. Part III speaks of obtaining the patent. Part IV of the patentee's rights under the law.

The table of cases and the Index indicates the large number of important cases which have relation directly or indirectly to the drug industries.

The Glossary of ten pages defines words and phrases most commonly used in patent law. The author states that no attempt has been made to give exact legal definitions or explanations but rather to translate such terms into concise English so that they may be understood and used by the reader.

A Table of Contents shows that the book is divided into twenty-one chapters and has been divided for study and presentation.

The makeup of the book shows the usual care given by the publishers.

The Law of Drugs and Druggists. A treatise with text, cases, statutes, readings and digests for schools of pharmacy, retail, wholesale and manufacturing druggists, by WILLIAM R. ARTHUR, Professor of Law at the University of Colorado, published by West Publishing Co., St. Paul. Price $3.00.

The volume is dedicated to his friend, Col. Homer C. Washburn, dean of the School of Pharmacy, University of Colorado. It is stated in the Preface that the volume was commenced many years ago by Dean Washburn and the author of the volume but not completed until recently. Professor Arthur has been giving a short course on Drug Law to the Senior classes of the School of Pharmacy of the University of Colorado, largely reviews of cases and the text is largely the result of these studies in analyzing litigations and cases in courts to bring out important details of laws relating to Pharmacy and allied branches. The book is divided into three parts: the first is a presentation of state and local laws; the second part of Federal statutes and regulations; and the third, in the form of an appendix, includes further references to food and drug legislation, narcotic and poison laws. The table of cases, cited and discussed, covers ten two-column pages. The list is followed by a Glossary explaining the terms and definitions in law procedure. Sixty pages are given to the Index.

The book is well printed and bound and will be found of value when information relative to laws of the drug trade and industries is needed.

SEPARATE FORMS OF THE ABSTRACT SECTION.

Extra forms of the Abstract Section can be supplied at 25 cents per set. This new service was begun in the March JOURNAL and will be continued each month. Order from the AMERICAN PHARMACEUTICAL ASSOCIATION, 2215 Constitution Ave., Washington, D. C.

FAIR TRADE MEASURES.

Governor La Follette, of Wisconsin, has signed the Alfonsi fair trade bill; the Iowa Legislature has adopted the Berg fair trade bill and transmitted it to Gov. Clyde L. Herring. Both the Wisconsin and the Iowa measures are based on the California Junior Capper-Kelly law. Pennsylvania, Maryland, New Jersey, New York and other states have taken similar action or contemplate perfecting such legislation.

NOTICE TO CONTRIBUTORS TO THE JOURNAL AMERICAN PHARMACEUTICAL ASSOCIATION.

The following notice has been prepared from comments received from members of the Board of Review of Papers and of the Publication Committee.

Manuscripts should be sent to Editor E. G. Eberle, 2215 Constitution Ave., N. W., Washington, D. C.

All manuscripts should be typewritten in double spacing on one side of paper $8^1/_2$ x 11 inches, and should be mailed in a flat package—not rolled. The original (*not* carbon) copy should be sent. The original drawings, not photographs of drawings, should accompany the manuscript. Authors should indicate on the manuscript the approximate position of text figures. All drawings should be marked with the author's name and address.

A condensed title running page headline, not to exceed thirty-five letters, should be given on a separate sheet and placed at the beginning of each article.

The method of stating the laboratory in which the work is done should be uniform and placed as a footnote at end of first page, giving Department, School or College. The date when received for publication should be given.

Numerals are used for figures for all definite weights, measurements, percentages, and degrees of temperature (for example: 2 Kg., 1 inch, 20.5 cc., 300° C.). Spell out all indefinite and approximate periods of time and other numerals which are used in a general manner (for example: one hundred years ago, about two and one-half hours, seven times).

Standard abbreviations should be used whenever weights and measures are given in the metric system, *e. g.*, 10 Kg., 2.25 cc., etc. The forms to be used are: cc., Kg., mg., mm., L. and M.

Figures should be numbered from 1 up, beginning with the text-figures (line engravings are always treated as text-figures and should be designed as such) and continuing through the plates. The reduction desired should be clearly indicated on the margin of the drawing. All drawings should be made with India ink, preferably on white tracing paper or cloth. If coördinate paper is used, a blue-lined paper must be chosen. Usually it is desirable to ink in the large squares so that the curves can be more easily read. Lettering should be plain and large enough to reproduce well when the drawing is reduced to the width of a printed page (usually about 4 inches). Photographs intended for half-tone reproduction should be securely mounted with colorless paste.

"Figure" should be spelled out at the beginning of a sentence; elsewhere it is abbreviated to "Fig.;" per cent—2 words.

The expense for a limited number of figures and plates will be borne by the JOURNAL; expense for cuts in excess of this number must be defrayed by the author.

References to the literature cited should be grouped at the end of the manuscript under the *References*. The citations should be numbered consecutively in the order of their appearance (their location in the text should be indicated by full-sized figures included in parentheses). The sequence followed in the citations should be: Author's name (with initials), name of publication, volume number, page number and the date in parentheses. Abbreviations for journals should conform to the style of *Chemical Abstracts*, published by the American Chemical Society.

(1) Author, A. Y., *Am. J. Physiol.*, 79, 289 (1927).

Papers presented at the Sections of the AMERICAN PHARMACEUTICAL ASSOCIATION'S annual meeting become the property of the Association and may at the discretion of the Editor be published in the JOURNAL. Papers presented at these Sections may be published in other periodicals only after the release of the papers by the Board of Review of Papers of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION.

The Editor will appreciate comments from Board of Review and Committee on Publication, members, authors and others interested.